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OCTOBER 1978

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

CUK-H01232-21-P024125 21

Surgery and Intraaortic Balloon Therapy for Unstable Angina

Controversies: Value and Limitations of Exercise Stress Testing

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logical therapy for the vast
who need more or other



Logical therapy because essential hypertension is usually characterized by elevated peripheral resistance with normal cardiac output. ALDOMET lowers blood pressure apparently by lowering peripheral resistance—while cardiac output is usually maintained.

Appropriate for all degrees of hypertension when drug therapy is required

Highly effective in mild, moderate, or severe hypertension, ALDOMET (Methyldopa, MSD) is useful when there has been an inadequate response to initial thiazide therapy, or as initial therapy when thiazides are deemed inappropriate or contraindicated (for example, when hypersensitivity to sulfonamide-derived drugs exists).

Appropriate for many hypertensive patients requiring special consideration

- hypertensive patients with renal impairment—ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. (Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.)
- hypertensive children requiring drug therapy (See pediatric dosage recommendations in the addendum on the last page of this advertisement.)

Not contraindicated in the following coexisting conditions in which some other antihypertensives are contraindicated

- congestive heart failure (Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses methyldopa should be discontinued.)
- coronary artery disease (Aggravation of angina pectoris may occur with ALDOMET.)
- mitral valvular rheumatic heart disease
- bronchial asthma
- allergic rhinitis during the pollen season
- greater than first-degree heart block
- active peptic ulcer
- ulcerative colitis

majority of hypertensives
therapy than a thiazide...



Therapeutic limitations

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, please see the brief summary of prescribing information.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

Logical therapy for the vast majority of hypertensives who need more or other therapy than a thiazide

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

JBAM17(709)

P 24,125

addendum

MSD MERCK SHARP DOHME

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- if effective control of blood pressure cannot be maintained on 2.0 g methyldopa daily and a thiazide is not already part of the regimen, a thiazide should be added
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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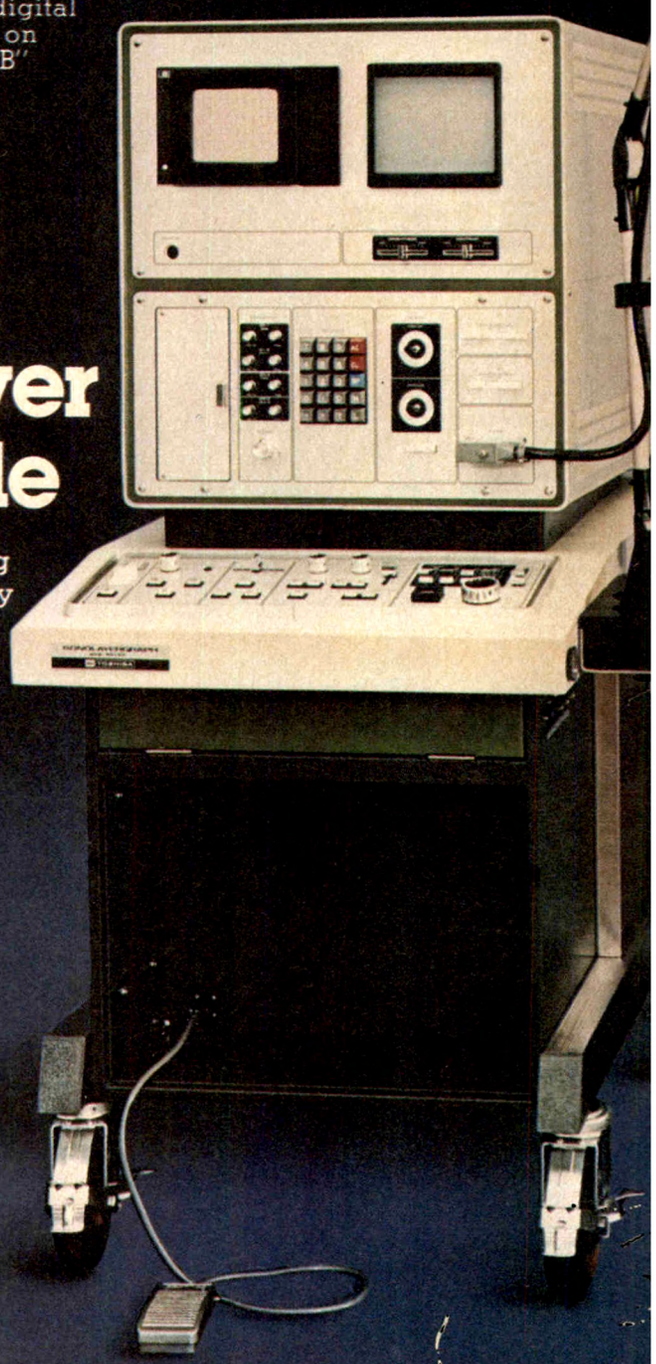
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THE AMERICAN JOURNAL OF CARDIOLOGY.® Official Journal of the American College of Cardiology, October 1978, Vol. 42, no. 4.

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published monthly, except May, semimonthly, by Technical Publishing Company, a Division of Dun-Donnelley Publishing Corporation, a Dun & Bradstreet Co. James B. Tafel, Chairman, John K. Abely, President. Executive, Editorial and Advertising Offices: 666 Fifth Avenue, New York, NY 10019. Printed in Easton, PA.

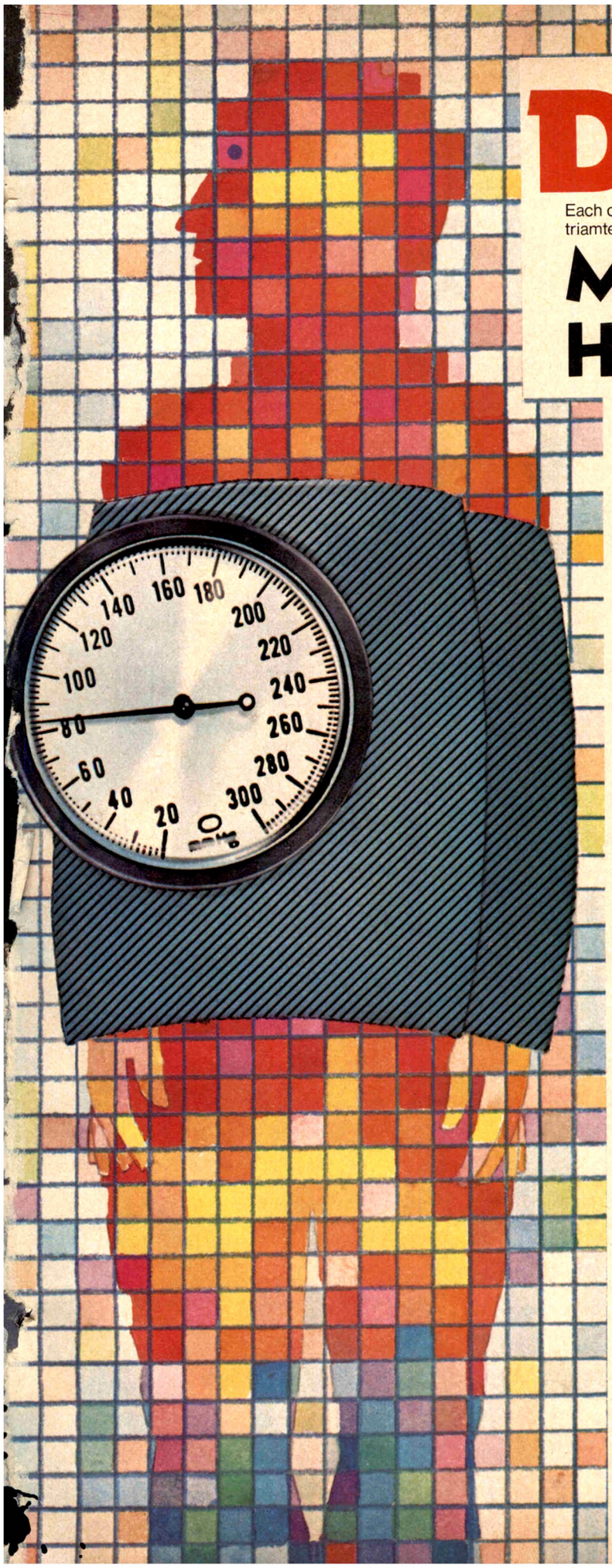
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* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

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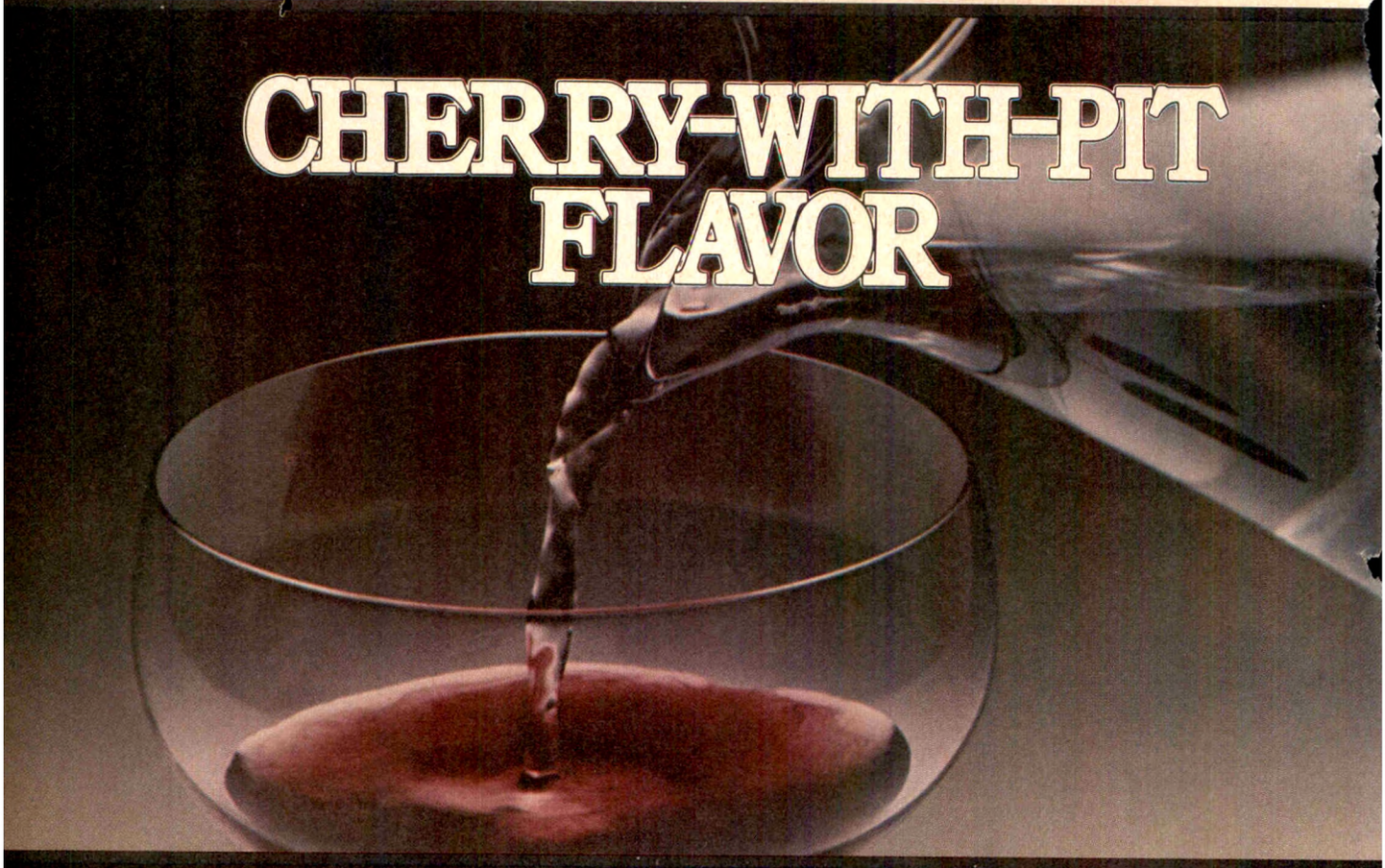
Persantine is a non-nitrate coronary vasodilator, with no known contraindications, for the long-term therapy of chronic angina pectoris.* The key to Persantine efficacy *give enough...long enough*

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Convenience in therapeutic doses. Both forms of KLORVESS offer 20 mEq of potassium and chloride in each dose. There is no need to prescribe several slow-release tablets per dose or space dosage administration beyond the patient's normal routine. Prescribe KLORVESS Liquid or KLORVESS Effervescent Tablets . . . for potassium supplement therapy that offers good taste and convenience at therapeutic dosages.

Description: Klorvess Effervescent Tablets: Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g. Dissolution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving alcosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

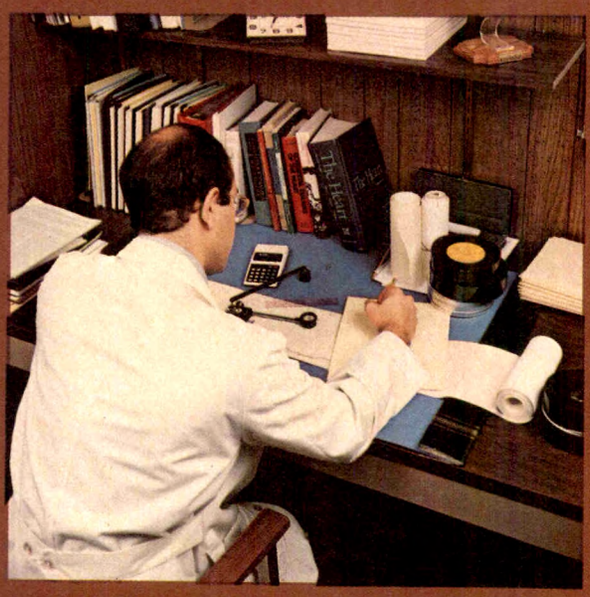
Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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OCTOBER 1978

The American Journal of CARDIOLOGY®

VOLUME 42

NUMBER 4

CONTENTS

CLINICAL STUDIES

533 Detection of Critical Coronary Lesions With Treadmill Exercise Testing: Fact or Fiction?

RAFAEL LEVITES and GARY J. ANDERSON

Treadmill tests performed according to the Bruce protocol produced S-T segment depression of 2 mm or more in 82 percent of patients with left main coronary artery disease and in 71 percent of patients with left main equivalent lesions. Half of the 37 patients with this degree of S-T segment depression had noncritical lesions. Ischemic changes in the first 3 minutes of exercise occurred in 63 percent of the patients with left main coronary disease and in 35 percent of the patients with left main coronary equivalent lesions. These results suggest that the value of stress testing as a predictor of critical coronary disease can be enhanced by considering both marked S-T segment depression and an ischemic response during the first 3 minutes of exercise. However, S-T depression of 2 mm or more is not a good indicator of critical coronary lesions because it has a low level of specificity. The time of onset of ischemic changes is useful but does not permit a definitive diagnosis in individual patients.

539 Hemodynamic and Anatomic Determinants of Relative Differences in Amplitude of the Aortic and Pulmonary Components of the Second Heart Sound

PAUL D. STEIN, HANI N. SABBAH, DANIEL T. ANBE and FAREED KHAJA

Intraarterial sound and pressure measurements during cardiac catheterization reveal that the pulmonary component of the second heart sound may equal or exceed the aortic component in patients with pulmonary hypertension. Both the pulmonary and aortic components of the second heart sound were affected by the rate of change of the pressure gradient; in patients with pulmonary hypertension, the rate of change of the pressure gradient and the pulmonary component of the second heart sound both increased. The normal pulmonary valve dissected at autopsy in 12 patients had a larger surface area and was more distensible than the normal aortic valve. These physical characteristics of the pulmonary valve also permit it to create more compression and more sound-pressure than the smaller and less distensible aortic valve.

545 Apparent Reduction of Aortic and Left Heart Chamber Size in Atrial Septal Defect

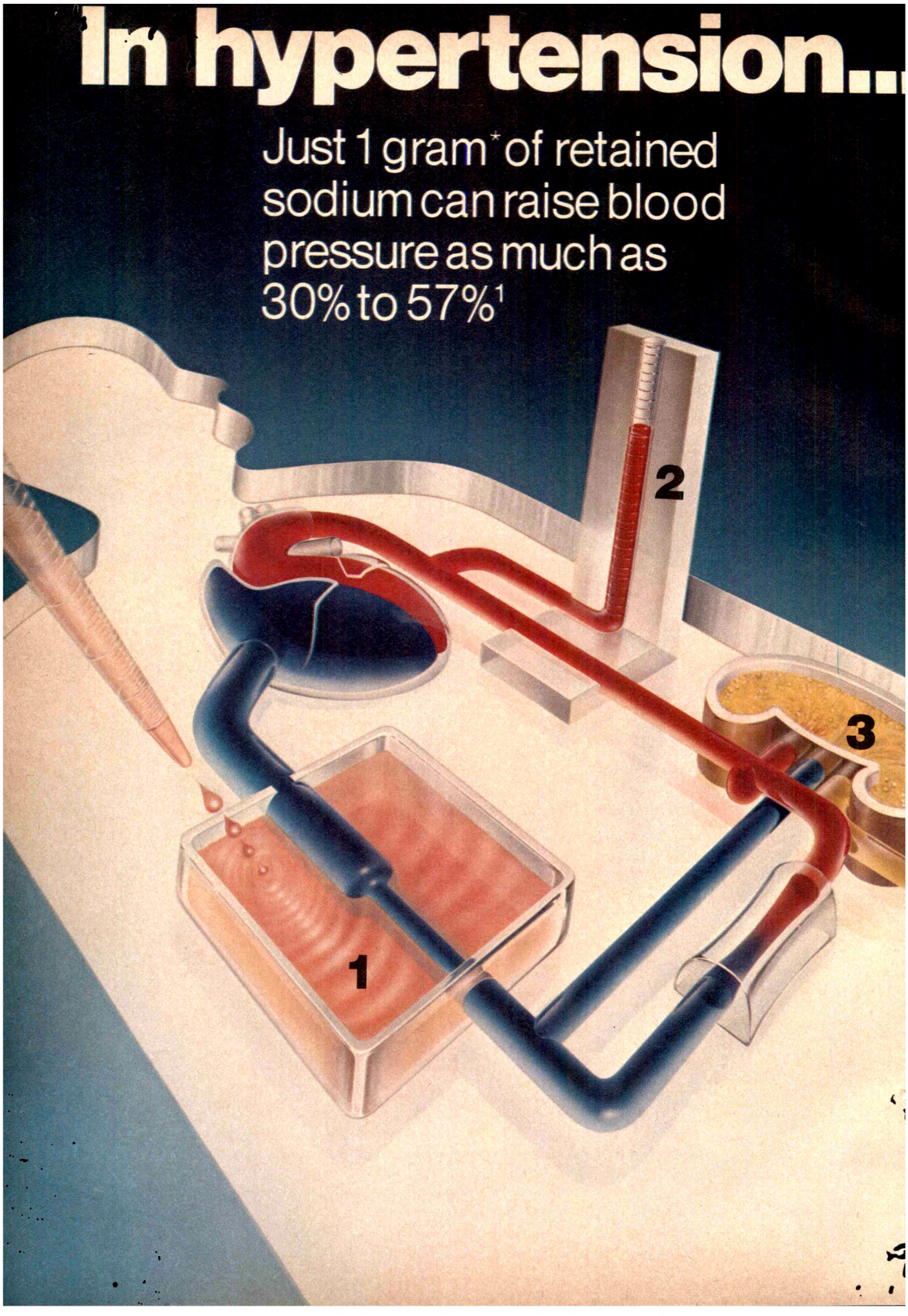
ANTHONY N. DeMARIA, LESLIE E. OLIVER, HUGO G. BORGREN, LILLY GEORGE and DEAN T. MASON

This study utilizing echocardiographic, cineangiographic and qualitative estimation of aortic size from chest X-ray films in 24 patients with atrial septal defect and in 22 normal subjects fails to support the clinical belief that the size of the aorta and left atrium is diminished in patients with an atrial septal defect, presumably because of a reduced stroke volume secondary to left to right shunting. These data also provide no evidence of a generalized reduction in left ventricular size due to underfilling of the cardiac chamber. The decreased left end-diastolic dimension recorded on echocardiography is a reflection of flattening or bowing of the interventricular septum caused by right ventricular enlargement.

Continued on page A15

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*All values given in this example are approximations based on standard physiologic data and solute-volume relationships.

†From a baseline of 80 mm. Hg diastolic.

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

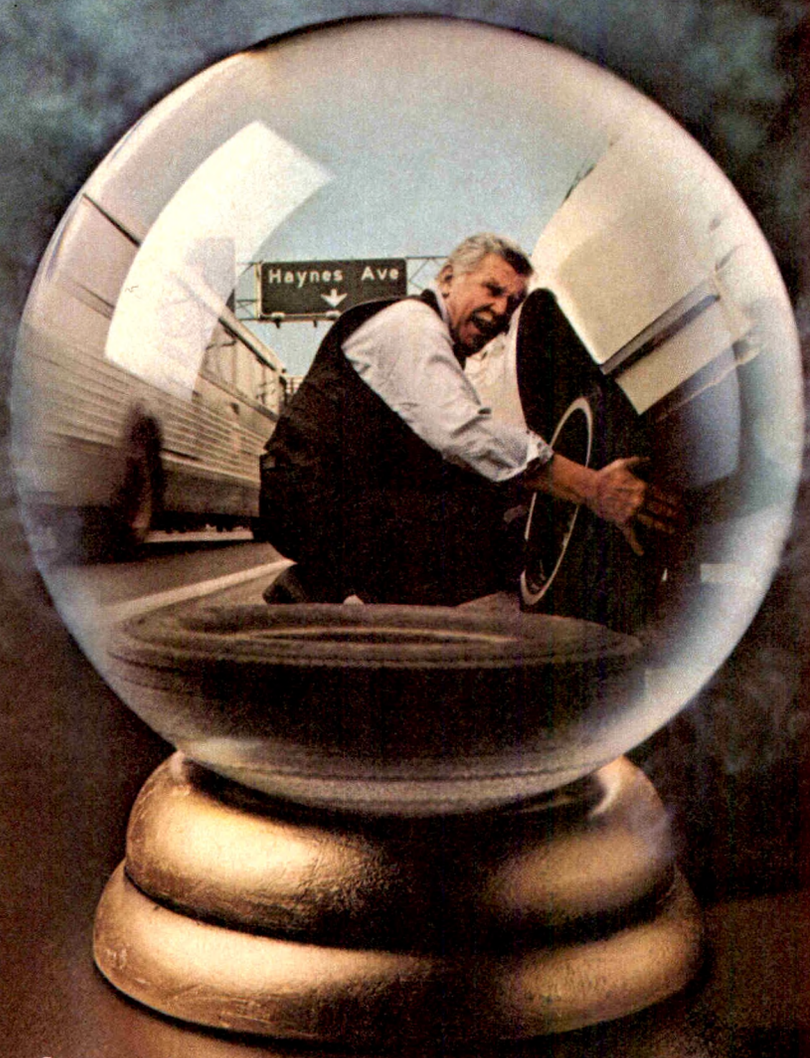
Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Guyton, A.C.: Regulation of arterial pressure: II. The renal-body fluid system for long-term pressure control. Mechanisms of hypertension, in Textbook of Medical Physiology, Philadelphia, Saunders, 1976, p. 281. **2.** Kaplan, N.: Treating hypertension: The results are in, in Mandates Hypertension (Kaplan, N.M., ed.), New York, Medcom, 1976, p. 6. **3.** Finnerty, F.A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20-23, 1976. **4.** Fries, E.D.: The treatment of hypertension: Why, when and how, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, p. 751. **5.** Tarazi, R.C.: Modern concepts in diuretic therapy, Postgrad. Med. 56:37, 1974.

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...during episodes of emotional stress or physical exertion

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE® (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

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CONTENTS

551 Significance of Left Axis Deviation in Patients With Chronic Left Bundle Branch Block

RAMESH C. DHINGRA, FERNANDO AMAT-Y-LEON, CHRISTOPHER WYNDHAM, SIVRAM S. SRIDHAR, DELON WU, PABLO DENES and KENNETH M. ROSEN

In a study of 102 patients with chronic left bundle branch block, 49 patients with a normal frontal axis and 53 with left axis deviation were compared. The group with left axis deviation were older and had a greater frequency of exertional angina, congestive heart failure, cardiomegaly, cardiac functional class II to IV, coronary artery disease and organic heart disease. Atrioventricular block developed in three patients with left axis deviation but in no patient with a normal axis. The 4 year mortality rate for the entire group approached 75 percent, but cardiovascular mortality was greater for the patients with than without axis deviation.

557 Cardiac Biopsy Evidence for a Cardiomyopathy Associated With Symptomatic Mitral Valve Prolapse

JAY W. MASON, FRANCIS H. KOCH, MARGARET E. BILLINGHAM and ROGER A. WINKLE

Right ventricular endomyocardial biopsy in 14 symptomatic patients with primary mitral valve prolapse showed a variety of pathologic changes. These included an increase in endocardial and interstitial fibrosis, mitochondrial degeneration, nuclear chromatin clumping, intercell edema and myocyte degeneration. These patients also had a large incidence of electrocardiographic abnormalities of the S-T segment and T wave and arrhythmias of the ventricular and supraventricular types. None of the eight patients who underwent coronary arteriography had significant coronary arterial narrowing. These findings favor the coexistence of a myocardial disease process in some symptomatic patients with idiopathic mitral valve prolapse.

563 Effect of Digoxin on Coronary Blood Flow and Myocardial Oxygen Consumption in Patients With Chronic Coronary Artery Disease

VOLKER KÖTTER, KLAUS-PETER SCHÜREN and ROLF SCHRÖDER

The intravenous injection of 1.0 mg of digoxin into 10 patients with chronic coronary artery disease and no clinical evidence of congestive heart failure improved left ventricular performance at rest and during stress. An increase in myocardial oxygen consumption due to enhanced contractility was completely counterbalanced most probably by a decrease in left ventricular volume after digoxin. Some deficiency in left ventricular function is probably present in some patients with chronic coronary artery disease even without clinical evidence of congestive heart failure. The authors believe it is therefore reasonable to try digitalis in patients with coronary artery disease and limited exercise tolerance due to decreased cardiac contractile reserve even in the absence of overt congestive heart failure.

570 Effects of Digitalis on Atrial Vulnerability

TOBY R. ENGEL and ANA DEL C. GONZALEZ

Repetitive atrial firing initiated by post-drive atrial extrastimulation was used to test the effects of digitalis (ouabain) on vulnerability to atrial fibrillation and flutter in nine patients without heart failure or significant mitral valve disease. When repetitive firing was manifested by flutter, neither the flutter cycle length nor the interval from the initiating beat to the first flutter beat was consistently altered by ouabain. The functional refractory period was lengthened after ouabain, and partly for this reason the vulnerable zone for the initiation of atrial fibrillation and flutter was shortened by ouabain. Ouabain did not shorten the atrial refractory period and had an inconsistent effect on atrial conduction. Atrial flutter, when it occurred, was almost invariably initiated after administration of ouabain, whereas atrial fibrillation sometimes occurred before administration of ouabain.

577 Pulmonary Pulsus Alternans in Acute Myocardial Infarction

JOSE LOPEZ-SENDON, ISABEL COMA-CANELLA, LUIS MARTIN JADRAQUE and ISIDORO GONZALEZ MAQUEDA

Hemodynamic monitoring of 100 consecutive patients with acute myocardial infarction revealed eight patients with pulmonary pulsus alternans. These patients had a smaller cardiac index, stroke volume and left ventricular stroke work index and higher pulmonary resistance and mortality rate than a control group of 30 patients without pulmonary alternans but with heart failure. The appearance of pulmonary pulsus alternans was associated with a decrease in cardiac index and an increase in pulmonary pressure and resistance levels. Its disappearance

Continued on page A17

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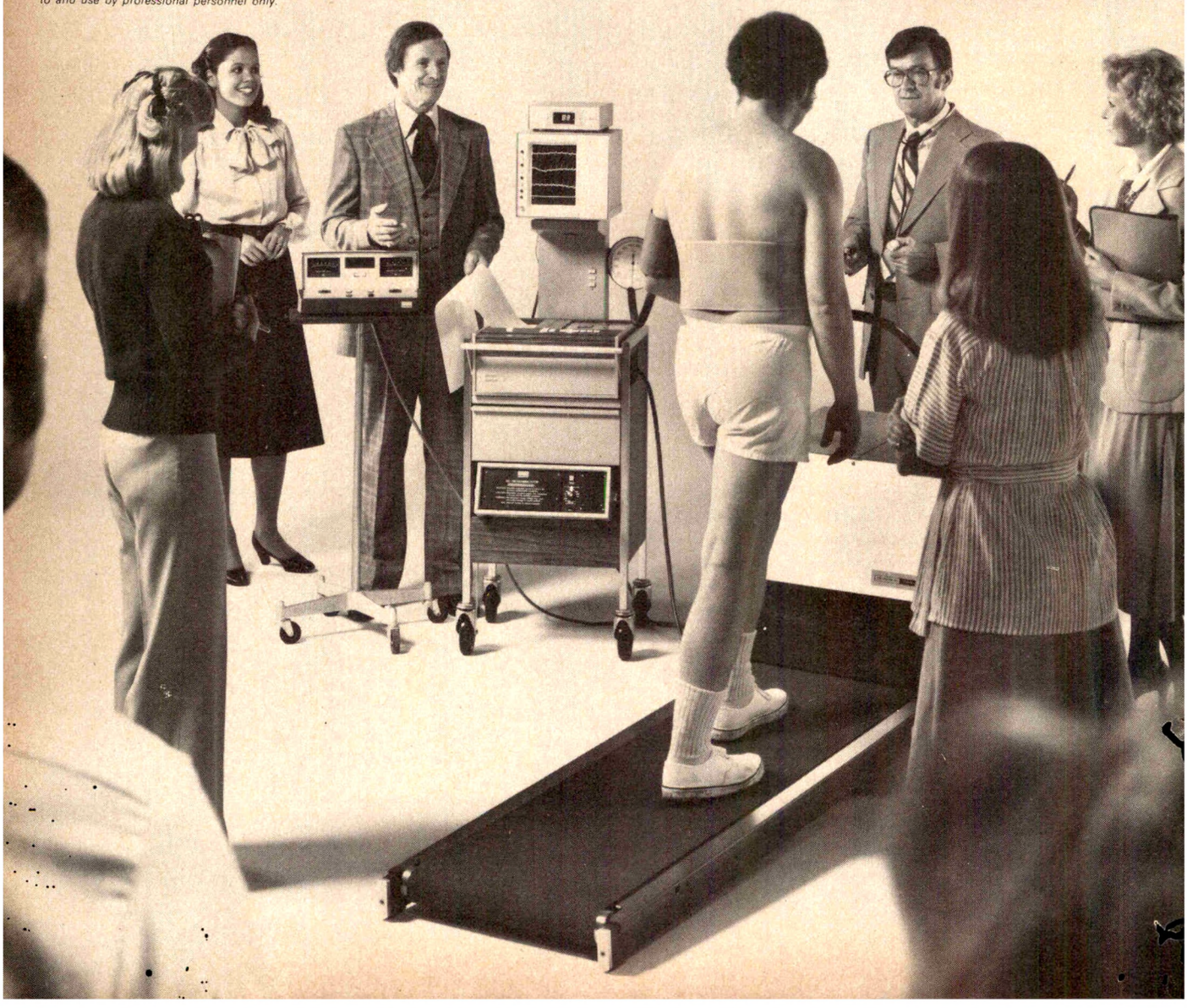
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sometimes followed a drug-induced decrease in pulmonary pressure and resistance levels and an increase in cardiac index. At other times it occurred after the administration of inotropic agents, without changes in pulmonary pressure. The study indicates that pulmonary pulsus alternans in acute myocardial infarction may appear under two conditions: (1) right ventricular strain secondary to left heart failure; and (2) impaired right ventricular contractility. The patients with alternans who died were in worse condition than the patients with alternans who survived, thus indicating that prognosis depends on the degree of heart failure rather than on the pulmonary pulsus alternans itself.

583 Type A Personality and Extent of Coronary Atherosclerosis

JOEL E. DIMSDALE, THOMAS P. HACKETT, ADOLPH M. HUTTER, Jr., PETER C. BLOCK and DONNA CATANZANO

In a study of 109 patients who underwent selective coronary arteriography, the authors found no relation between type A personality, as measured with the Jenkins Activity Survey score, and the extent of coronary artery disease (vessels with 50 percent or greater narrowing of diameter). It is possible that assessments of type A personality with the interview method may show a greater correlation with the extent of coronary disease found at cardiac catheterization.

EXPERIMENTAL STUDIES

587 Effect of Lidocaine on Conduction in the Ischemic His-Purkinje System of Dogs

GARY GERSTENBLITH, BENJAMIN J. SCHERLAG, RONALD R. HOPE and RALPH LAZZARA

After experimentally produced ischemic damage to the His bundle in dogs by ligation of the anterior septal artery, the administration of lidocaine significantly increased the H-V time and resulted in advanced His-Purkinje conduction defects including His bundle branch and right bundle branch block. These results demonstrate that lidocaine significantly depresses His-Purkinje conduction in the presence of ischemic damage and suggest that it may serve as a diagnostic tool to detect latent His-Purkinje conduction defects due to ischemia. In patients with a suspected A-V conduction defect secondary to acute myocardial infarction, the use of His bundle recordings performed during the stress of atrial pacing and lidocaine may possibly identify more precisely those patients with latent disease at greater risk of sudden death due to cardiac asystole.

PEDIATRIC CARDIOLOGY

592 Anatomic Types of Congenital Mitral Stenosis: Report of 49 Autopsy Cases With Consideration of Diagnosis and Surgical Implications

ROGER N. RUCKMAN and RICHARD VAN PRAAGH

A series of 49 autopsy cases of congenital mitral stenosis revealed four anatomic types: (1) 24 cases of typical congenital mitral stenosis with short chordae tendineae, obliteration of interchordal spaces and reduction of interpapillary distance; (2) 20 cases of hypoplastic congenital mitral stenosis, almost always associated with a hypoplastic left heart syndrome; (3) 6 cases of supramitral ring; and (4) 4 cases of parachute mitral valve. Death occurred at 6 months and 5 days, respectively, in the first and second groups and at 5 6/12 and 9 11/12 years in the latter two groups. Associated malformations, found in 96 percent, included endocardial sclerosis or florid endocardial fibroelastosis, hypoplasia of the aortic isthmus, aortic valve stenosis, aortic atresia and coarctation of the aorta. Real time two dimensional echocardiography should make possible the differential diagnosis of these four anatomic types. Mitral valvuloplasty appears to be the initial surgical procedure of choice, and mitral valve replacement should be deferred as long as possible.

602 Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy in the Presence of Right Bundle Branch Block in Young Subjects

CHRISTIAN R. BROHET, MADY STYNS, PIERRE ARNAUD and LUCIEN A. BRASSEUR

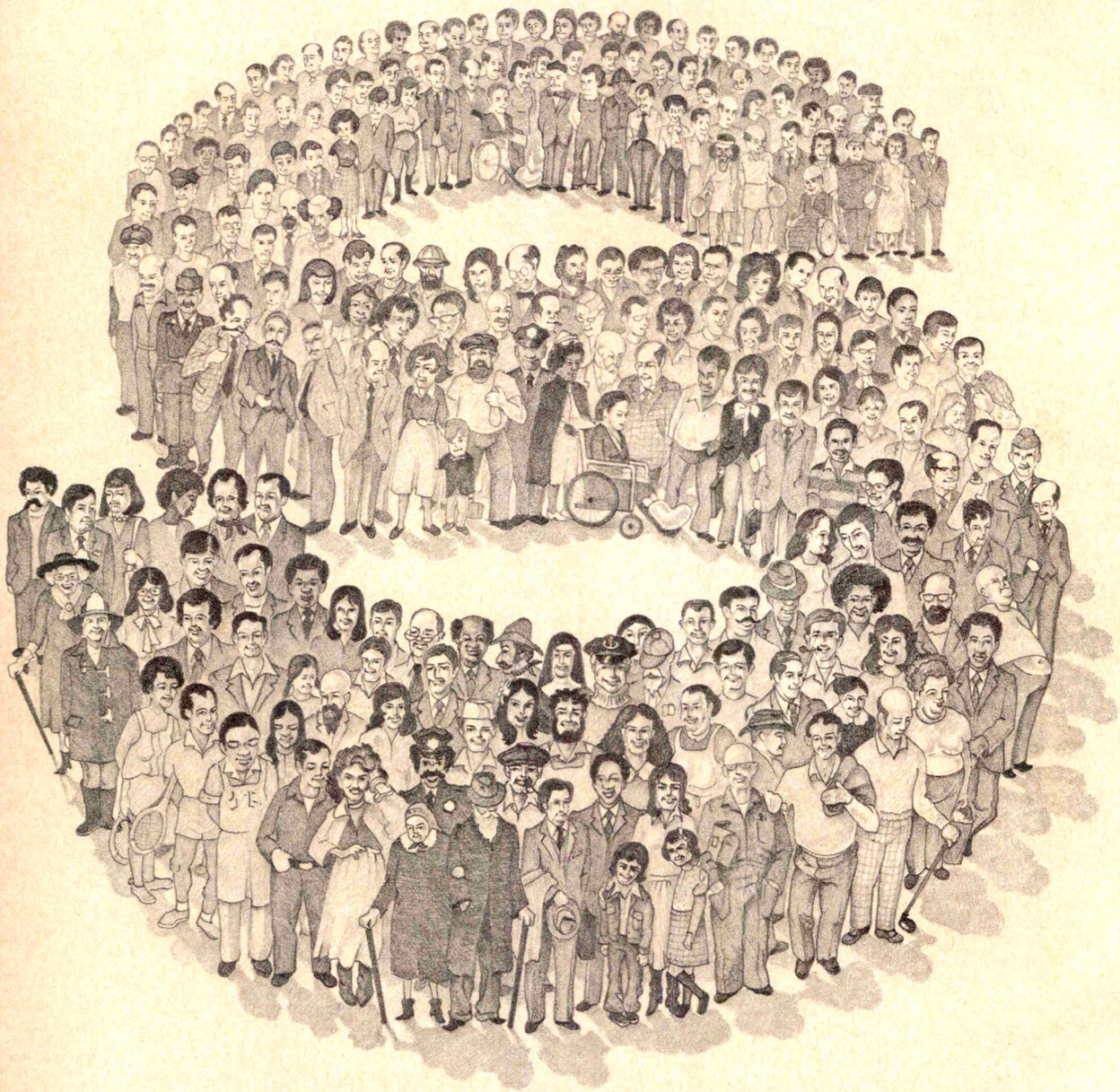
Clearly demonstrating the value of quantitative analysis of the vectorcardiogram in diagnosing right ventricular hypertrophy combined with right bundle branch block, this study easily separated the patients with right bundle branch block alone from those with right bundle branch block and right ventricular hypertrophy. The most useful criterion was the ratio between the magnitude of the R wave and that of the S wave (R/S ratio) in lead X. The

Continued on page A19

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morphologic criteria were less able to differentiate between the two groups of patients. In young patients with surgically induced right bundle branch block any one of the following vectorcardiographic criteria suggest the presence of concomitant right ventricular hypertrophy: (1) a clockwise rotation of the QRS loop in the horizontal plane; (2) an R/S ratio of the R and S waves in lead X of less than 2.0; (3) a maximal QRS vector in the horizontal plane located between 90° and 270°; or (4) a mean QRS vector in lead X more negative than −10 mv·msec.

613 Maximal Exercise Capacity of Children With Heart Defects

GORDON R. CUMMING

Comparing the results of 830 consecutive maximal treadmill exercise tests performed by children with heart defects with those of normal children with a normal heart attending the same clinics, this study found that only 21 percent of the children with heart defects had an endurance time below the 10th percentile line. This line was 14 percent higher in the normal schoolchildren, and 47 percent of the patient group had values below the 10th percentile when values in schoolchildren were used as reference. Maximal exercise tests do not necessarily distinguish between children with mild and severe heart disease. Only children with lesions causing cyanosis or those with obviously severe disease have consistent reductions in exercise capacity.

620 The Criss-Cross and Superoinferior Ventricular Heart: An Angiocardiographic Study

ROBERT M. FREEDOM, GORDON CULHAM and RICHARD D. ROWE

This angiographic study of 11 patients with superoinferior and criss-cross type of atrioventricular (A-V) connections suggests the unusual ventricular relations result from postseptation disturbances of ventricular looping. The angiographic appearance of criss-cross is an illusion, and the A-V connections among these patients are either concordant, discordant or straddling. The often small right A-V valve inflow and sinus portion of the ventricle, combined with the ventricular rotational anomaly, combine to give the angiographic appearance of criss-cross. Most patients with this finding have a transposition or malposition of the great arteries; many have a small right ventricle, and about half have pulmonary outflow tract obstruction. These findings raise questions about the various segmental nomenclatures applied to these types of congenital heart disease.

REPORTS ON THERAPY

629 Surgical Approach for Patients With Unstable Angina Pectoris: Role of the Response to Initial Medical Therapy and Intraaortic Balloon Pumping in Perioperative Complications After Aortocoronary Bypass Grafting

RENE A. LANGOU, ALEXANDER S. GEHA, GRAEME L. L. HAMMOND and LAWRENCE S. COHEN

This study of 194 consecutive patients with unstable angina pectoris undergoing coronary bypass surgery demonstrates that the combination of initial aggressive medical therapy and the preoperative insertion of an intraaortic balloon pump decreases the rate of both operative mortality and perioperative myocardial infarction. In this group the overall rate of operative mortality was 6.1 percent and the overall incidence rate of perioperative myocardial infarction was 13 percent. Medical management included absolute bed rest, sedation, reassurance and relief of pain with narcotic drugs in addition to long- and short-acting nitrates and large doses of propranolol. The average daily dose of propranolol was 380 ± 50 mg after full medical therapy in the coronary care unit. The dose of propranolol was rapidly increased until the angina was completely relieved, the patient's resting heart rate was 50 to 55 beats/min or there was clinical evidence that the heart failure could not be controlled with standard therapy.

634 Unstable Angina: The Case for Operation

GORDON N. OLINGER, LAWRENCE I. BONCHEK, MICHAEL H. KEELAN, Jr., DONALD D. TRESCH, RONALD SIEGEL, VIRINDERJIT BAMRAH and FELIX E. TRISTANI

The results of surgical revascularization performed from July 1975 through September 1977 in 95 consecutive patients with unstable angina, more than half at high risk, indicate the consistent improvements being made in the surgical treatment of coronary artery disease. Patients at high risk required large doses of propranolol and one patient needed additional intraaortic counterpulsation for preoperative stabilization of ischemia. Proximal left anterior descending and left main coronary artery disease with abnormal ventricular function characterized

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both the high and low risk groups. One death and three perioperative infarctions occurred. No patient needed inotropic support, and no late deaths occurred in a follow-up period of 30 months. The data indicate that (1) "prophylactic" preoperative intraaortic balloon counterpulsation is not necessary in patients with unstable angina; (2) there is a small risk of complications when unstable angina is appropriately managed; and (3) results of large scale studies of unstable angina performed several years ago may not be relevant to therapeutic decisions made in 1978.

EPIDEMIOLOGY

641 Congenital Heart Disease in a Cohort of 19,502 Births With Long-Term Follow-Up

JULIEN I. E. HOFFMAN and ROBERTA CHRISTIANSON

In this study of 19,502 births, 163 of the 19,044 live born children had definite and another 31 possible congenital heart disease. The crude incidence rates per 1,000 live births were 8.8 for definite congenital heart disease and 10.4 for definite plus possible congenital heart disease. The incidence rate of congenital heart disease was 7.9 percent among all autopsies in stillborn fetuses and 10.2 percent among autopsies in this group evaluated as being detailed enough to detect heart disease. Among the 163 children with definite congenital heart disease, the diagnosis was made in 46 percent by age 1 week, in 88.3 percent by age 1 year and in 98.8 percent by age 4 years. The data emphasize the need for better evaluation of congenital heart disease in abortuses and stillborn infants and for the development of better methods of identifying minimal heart disease. More complete case findings would lead to more exact incidence data but also to more precise correlation with genetic and environmental factors and thus allow better understanding of the causes of congenital heart disease.

648 Survival of Patients With Nontransmural Myocardial Infarction: A Population-Based Study

MOYSES SZKLO, ROBERT GOLDBERG, HAROLD L. KENNEDY and JAMES A. TONASCIA

In this population-based study conducted in metropolitan Baltimore, the short- and long-term prognoses of 283 patients with nontransmural and 953 patients with transmural myocardial infarction were compared. The adjusted in-hospital case fatality rate was greater in patients with transmural than with nontransmural infarction, but no significant differences in survival between the two patient groups were found among those discharged alive from the hospital and followed up for as long as 10 years. The adjusted 3 year case fatality rate was 27.1 and 28.3 percent, respectively, for patients in the two groups who survived the acute phase. Thus, the long-term prognosis of patients with nontransmural infarction appears to be as guarded as that of patients with transmural infarction, and attempts to prevent subsequent mortality should be pursued with equal vigor in both groups.

653 Relation of Lipids, Weight and Physical Activity to Incidence of Coronary Heart Disease: The Puerto Rico Heart Study

RAUL COSTAS, Jr., MARIO R. GARCIA-PALMIERI, EMILIO NAZARIO and PAUL D. SORLIE

In this cohort of 8,171 urban and rural men 45 to 64 years old participating in the Puerto Rico Heart Program, a population with a low incidence rate of coronary heart disease, the risk of coronary disease was related to serum cholesterol levels in both urban and rural groups but this trend was statistically significant only in the urban population. Values for serum cholesterol, triglycerides and relative weight were all significantly higher in the urban men. Multivariate analysis revealed that only serum cholesterol was related to the risk of coronary heart disease even when all variables were taken into account. Low levels of physical activity were associated with increased risk of coronary heart disease only in urban dwellers and in the most sedentary men.

CONTROVERSIES: EXERCISE TESTING

659 Role of Exercise Stress Testing in Healthy Subjects and Patients With Coronary Heart Disease. Controversies in Cardiology—I

STEPHEN N. MORRIS and PAUL L. McHENRY

This comprehensive review discusses the current strengths and weaknesses as well as the important diagnostic and prognostic aspects of the exercise stress test, including the pitfalls to avoid. The reliability of the exercise test as a diagnostic tool is improved by proper patient selection, careful attention to exercise techniques and... changes such as abnormalities of the S-T segment, a decrease in systolic blood pressure during exercise, the

Continued on page A23



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appearance of complex ventricular arrhythmias at low exercise heart rates, the appearance of inverted U waves during or after exercise, the patient's maximal exercise capacity and new auscultatory findings postexercise. Attention is drawn to the greater incidence of false positive tests in women. The reliability of the test is enhanced when it is utilized selectively and the data interpreted appropriately.

667 **Values and Limitations of the Electrocardiographic Response to Exercise in the Evaluation of Patients With Coronary Artery Disease. Controversies in Cardiology—II**

STEPHEN E. EPSTEIN

This view of exercise testing suggests that the results provide a probability statement rather than a definitive answer regarding the existence of coronary artery disease and notes that in asymptomatic subjects (1) the S-T segment response to exercise has a relatively poor predictive accuracy, (2) exercise testing does not appear to be a practical screening method for detecting those at high risk of sudden death, and (3) risk factors should be rigorously treated regardless of the results of screening studies for coronary artery disease. The author argues that exercise testing does not provide enough diagnostic or prognostic information to justify routine use in asymptomatic subjects. In symptomatic patients it provides only marginal aid in detecting coronary artery disease but may provide important prognostic information that may be helpful in patient management.

DIAGNOSTIC SHELF

675 **Thallium-201 Myocardial Imaging in Anomalous Left Coronary Artery Arising From the Pulmonary Artery. Applications Before and After Medical and Surgical Treatment**

JOHN P. FINLEY, ROBERT HOWMAN-GILES, DAVID L. GILDAY, PETER M. OLLEY and RICHARD D. ROWE

Thallium-201 myocardial imaging performed in six patients, aged 4 months to 20 years, with an anomalous left coronary artery arising from the pulmonary artery proved useful in the diagnosis and follow-up of medical and surgical therapy of this condition. The procedure for monitoring changes in myocardial perfusion may shed light on the pathophysiology of the defect. A possible practical limitation is the difficulty of imaging subendocardial infarction.

681 **Electrocardiographic Pseudo-Infarction Pattern: Appearance With a Large Posterior Pericardial Effusion After Cardiac Surgery**

BAKR IBRAHIM SALEM, MARK SCHNEE, LOUIS L. LEATHERMAN, CARLOS M. de CASTRO and JAIME BENREY

Electrocardiographic precordial Q waves without evidence of myocardial infarction occurred in two patients with a large posterior pericardial effusion after cardiac surgery. Resolution of the pericardial fluid resulted in disappearance of the Q waves. Changes in conductivity and orientation of the heart within the pericardial space, together with a decrease in QRS voltage, could lead to the loss of initial R waves in the precordial leads, eventually resulting in a QS complex. The clinical course of patients and serial electrocardiographic and echocardiographic tracings should be helpful in identifying this pattern of false infarction in patients with a large posterior pericardial effusion after cardiac surgery.

EDITORIALS

686 **Oral Vasodilator Therapy for Chronic Heart Failure: A Plea for Caution**

MILTON PACKER and JOSE MELLER

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690 **Letters to the Editor**

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Sudden Death: How Unexpected?—J. E. Mielke and L. E. Hinkle, Jr.

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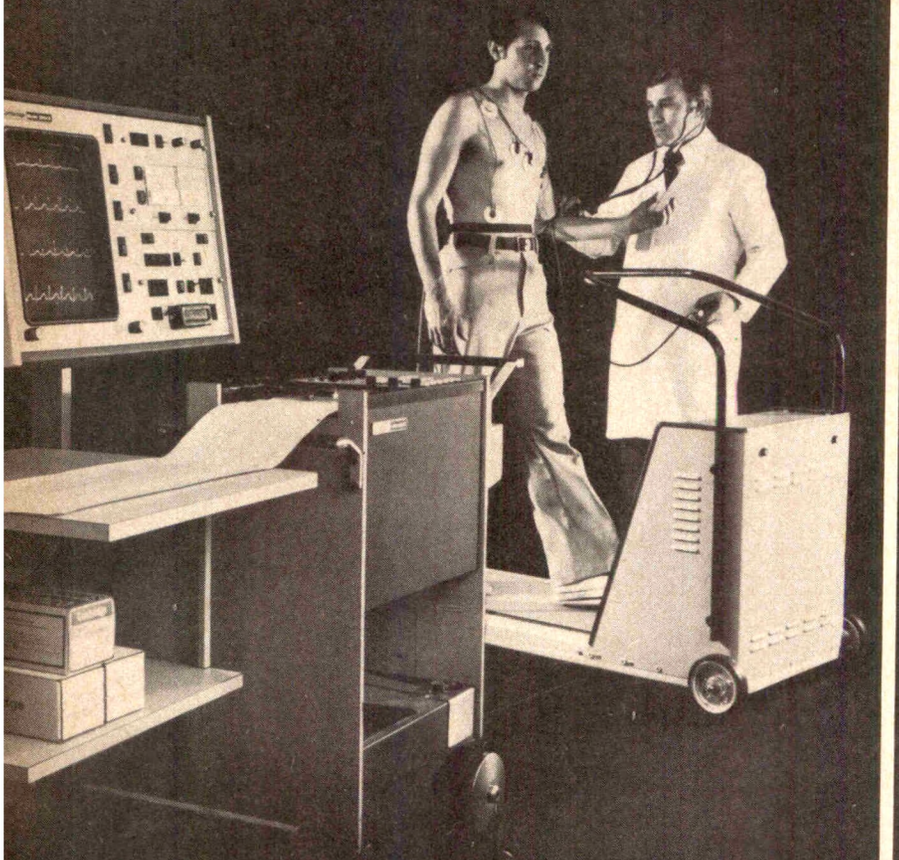
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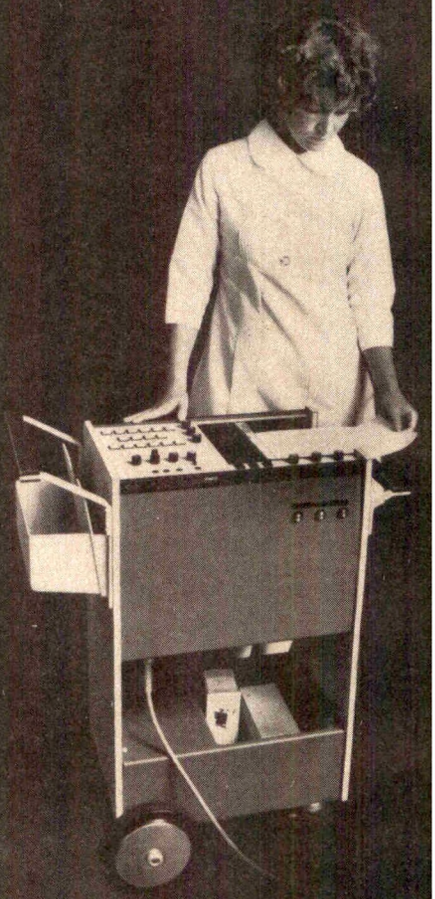
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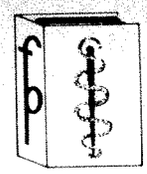
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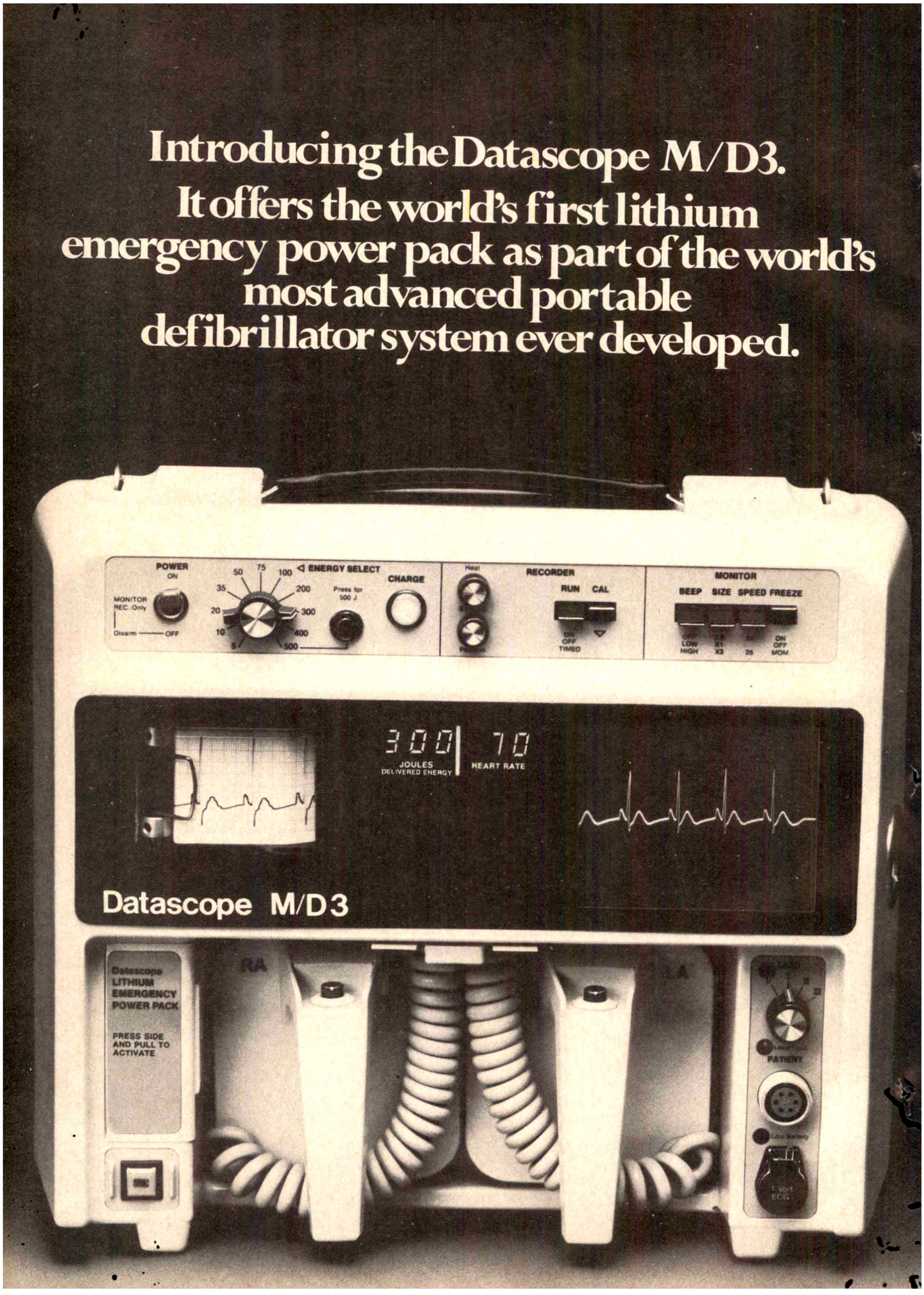
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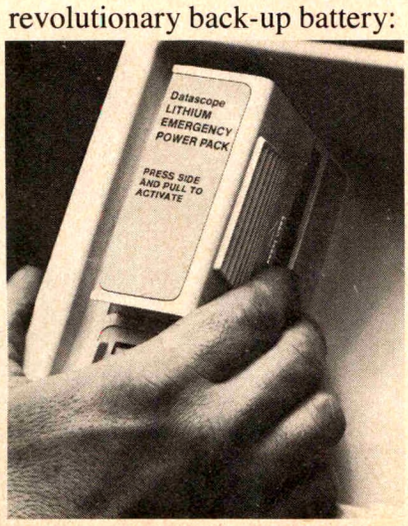
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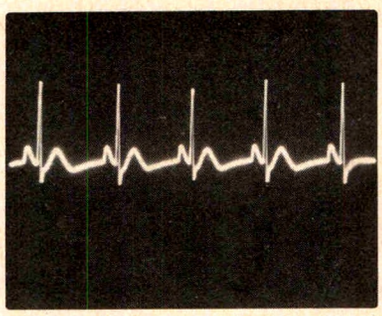
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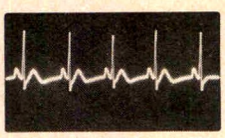


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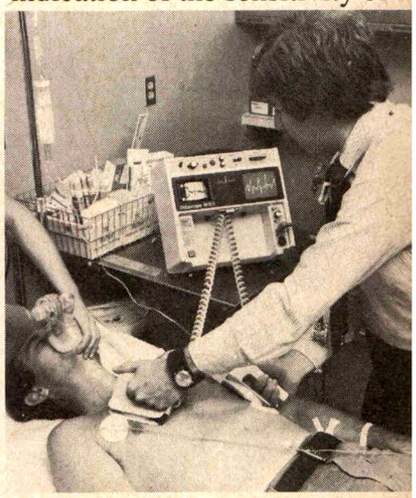
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To the electrode lead fault indicator

To the manner in which the battery pack can be rapidly ejected for replacement.

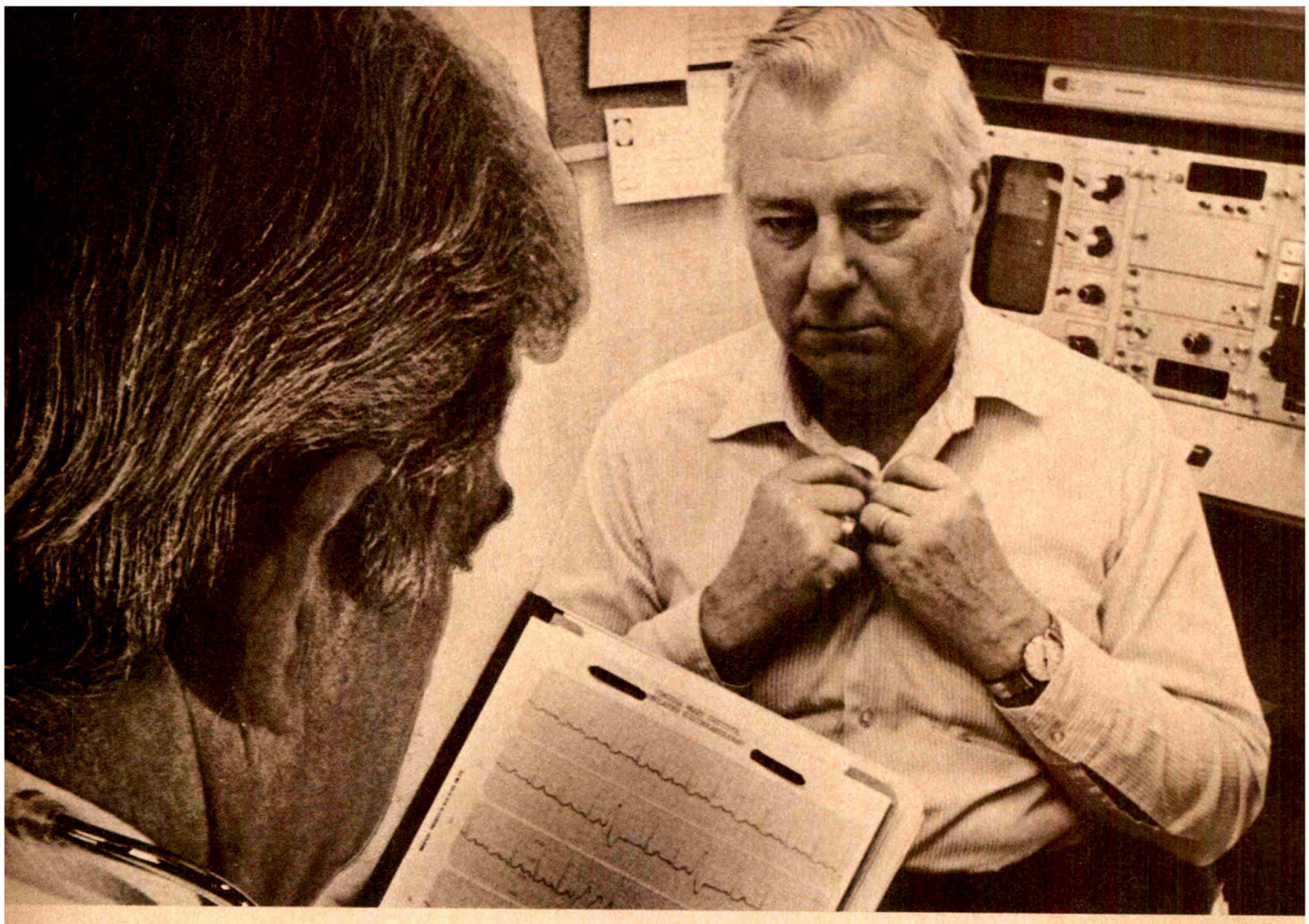
To the fact that batteries are recharged in less than 5 hours instead of the usual 16.

In short, the M/D3 is the most innovative development in defibrillator systems today.

Frankly, there are so many exciting features in the M/D3, there's simply not enough space to discuss them all here. We urge you to see the M/D3 first-hand. To arrange for a demonstration call us at 201 265-8800. Datascope Corp., Box 5-S Paramus, NJ. 07652

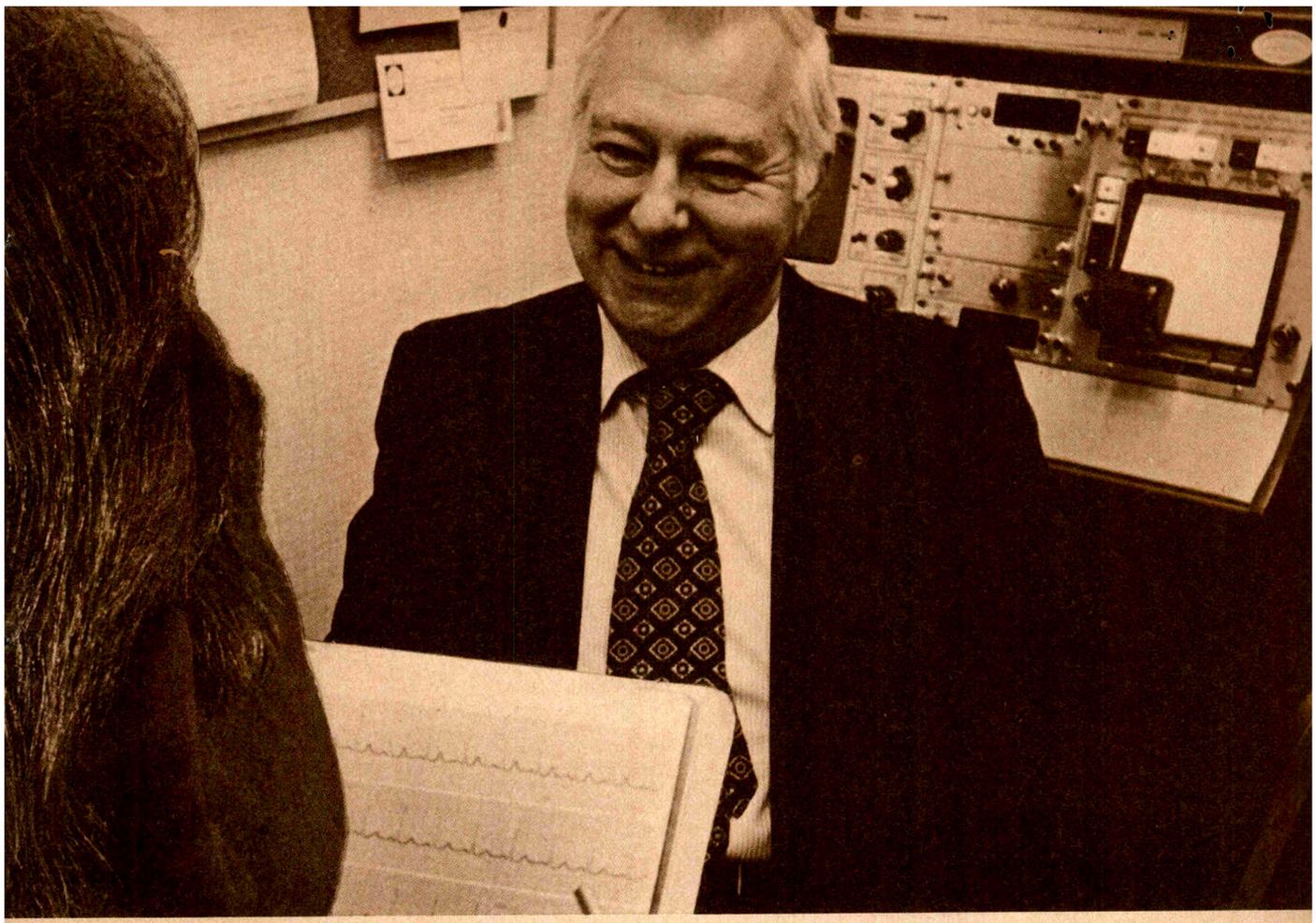
In Europe: Datascope B.V., Post Box 26, 3870 CA Hoevelaken, Holland.

The Datascope M/D3 Defibrillator System



Diagnosis: PVC's
(Premature Ventricular Contractions)

initial therapy:
quinidine sulfate tablets
at
9 a.m.
1 p.m.
5 p.m.
9 p.m.



Then, for convenience and compliance... a welcome change- simple q 8-12 hour dosage

Quinidex Extentabs®

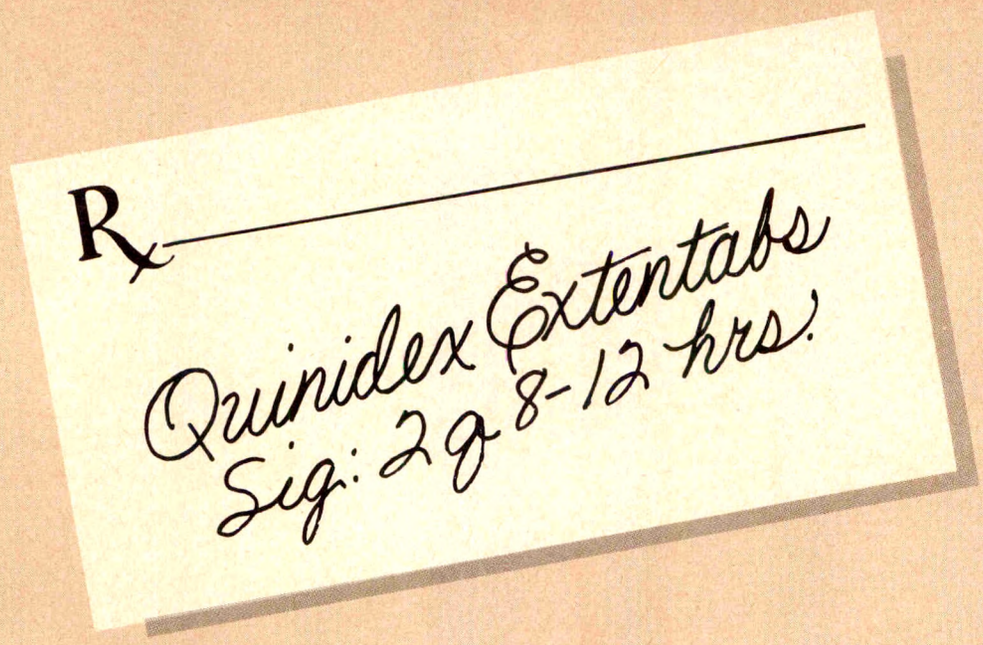
(Quinidine Sulfate, USP)

300 mg in each Extentab

A·H·ROBINS

After the PVC's have been successfully suppressed with quinidine sulfate tablets, you can *maintain* normal sinus rhythm with Quinidex Extentabs. The simple q 8-12 hour dosage is more convenient for the patient than the usual q.i.d. dosage for short-acting tablets. Instead of having to remember to carry his medication with him during the day, he simply leaves the bottle in the medicine cabinet. There's less risk of a missed dose . . . better compliance with your dosage regimen. The unique construction of Quinidex Extentabs provides continuous absorption of quinidine sulfate over an 8-12 hour period. Each of the Extentabs contains 300 mg quinidine sulfate – approximately 23% more quinidine alkaloid than 324 mg quinidine gluconate.

See full prescribing information on following page.



Indications:

Quinidex Extentabs are indicated in the treatment of:

Premature atrial and ventricular contractions.
Paroxysmal atrial tachycardia.
Paroxysmal A-V junctional rhythm.
Atrial flutter.
Paroxysmal atrial fibrillation.
Established atrial fibrillation when therapy is appropriate.
Paroxysmal ventricular tachycardia when not associated with complete heartblock.
Maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

The only long-acting form of quinidine sulfate

Quinidex® Extentabs

(Quinidine Sulfate, USP)

ROBINS

A·H·ROBINS

A. H. Robins Company, Richmond, Va. 23220

Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, lightheadedness, and tremor; (3) G-I symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at a rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G-I symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 and 250 (NDC 0031-6649).

Total·View patient monitoring



PDS 3000: complete patient information in a Total·View

GE offers you new technology in the microprocessor-based PDS 3000 patient monitoring system that allows you to react more quickly to patient conditions. That's because the central station presents all vital patient information on one display for clear, Total-View readability.

The central station display and message center provide simultaneous, alphanumeric presentation of up to ten parameters per patient—without repeater modules or complex switching. A continuous display of non-fade waveforms is included with independent freeze and cascade capability. Plus, the operator is immediately informed of all abnormal changes in patient and equipment conditions.

Strip chart recordings give you a permanent and complete record of data being measured. An alphanumeric edge printer identifies each recording by bed number, time, date, heart rate, lead configuration and blood pressure values for easier patient charting.

PDS 3000 bedside units are available in three or four module configurations. Each plug-in, pull-out module fits in any slot without the need for tools. This allows you to tailor the system to the needs of each patient—conveniently.

With PDS 3000 you have the reliability of the latest in monitoring technology and the convenience of Total-View patient information. Get all the facts. Contact your GE representative today.

General Electric Medical Systems,
Milwaukee, Toronto, Madrid.

100 Years of Progress for People

GENERAL ELECTRIC

A New Book! **PROGRESS IN CARDIOLOGY. 7.** *Edited by* PAUL N. YU, M.D., *University of Rochester School of Medicine and Dentistry, Rochester, New York; and* JOHN F. GOODWIN, M.D., *Royal Postgraduate Medical School, London, England. (Contributors).* This important, ongoing series has proven to be a very welcome source of clinical information for cardiologists and others with need for continuing knowledge of newer concepts in the field. *Volume 7* in this series follows the pattern established in preceding volumes by presenting recent advances and increasingly important aspects of cardiology. The chapters, written by an international group of eminent investigators and teachers in their chosen fields, cover topics that are timely and of broad base. All chapters contain a generous number of illustrations. *About 300 pp. (7 × 10), illus., 1978, Ready Now.*

A New Book! **CORONARY ARTERY SURGERY.** *By* JOHN L. OCHSNER, M.D., *and* NOEL L. MILLS, M.D., *both of the Ochsner Clinic, New Orleans, Louisiana.* Authoritative and complete in its treatment of the subject, this book encompasses many aspects of coronary artery disease. An abundance of precise, clinical information concerning use of the saphenous vein and the internal mammary artery as grafts, cannulation and extracorporeal circulation, type of operation and site of distal anastomosis, exposure of the heart, methods of vascular anastomoses, and management of complications is presented. Original drawings profusely illustrate these technical maneuvers. Anesthetic management and postoperative care are carefully outlined in a clear, step-by-step method. Psychological considerations of the patient are emphasized. *275 pp. (7 × 10), illus., 1978, $25.00.*

A New Book! **POLICIES AND PROCEDURES OF A CARDIAC REHABILITATION PROGRAM: Immediate to Long-term Care.** *By* PHILIP K. WILSON, Ed.D., *La Crosse Exercise Program, University of Wisconsin-La Crosse;* EDWARD R. WINGA, M.D. *and* JOSEPH W. EDGETT, M.D., *both of Gundersen Clinic, Ltd., and La Crosse Lutheran Hospital; and* THOMAS T. GUSHIKEN, Ph.D., *La Crosse Exercise Program, University of Wisconsin-La Crosse, La Crosse, Wisconsin.* Designed to serve the purpose of prevention, intervention, and rehabilitation, this manual is a complete description of all the procedures and policies of the La Crosse Cardiac Rehabilitation Program at the University of Wisconsin. All records and forms utilized in the daily operation of the program are included here. *253 pp. (7 × 10), 200 records and forms, paperback, 1978, Ready Now.*

DRUG TREATMENT: Principles and Practice of Clinical Pharmacology and Therapeutics. *Edited by* GRAEME S. AVERY, *Editor-in-Chief, Australasian Drug Information Services Pty Ltd., Sydney, Australia. (53 American and International Contributors).* This important book carefully describes the clinical pharmacological basis of therapeutics, rational selection and individual use of drugs, influence of associated disease, and drug-induced diseases. *1048 pp. (7 × 10¼), illus., tables, 1976, $29.50. (Distribution rights limited to North, Central and South America and Japan.)*

For current

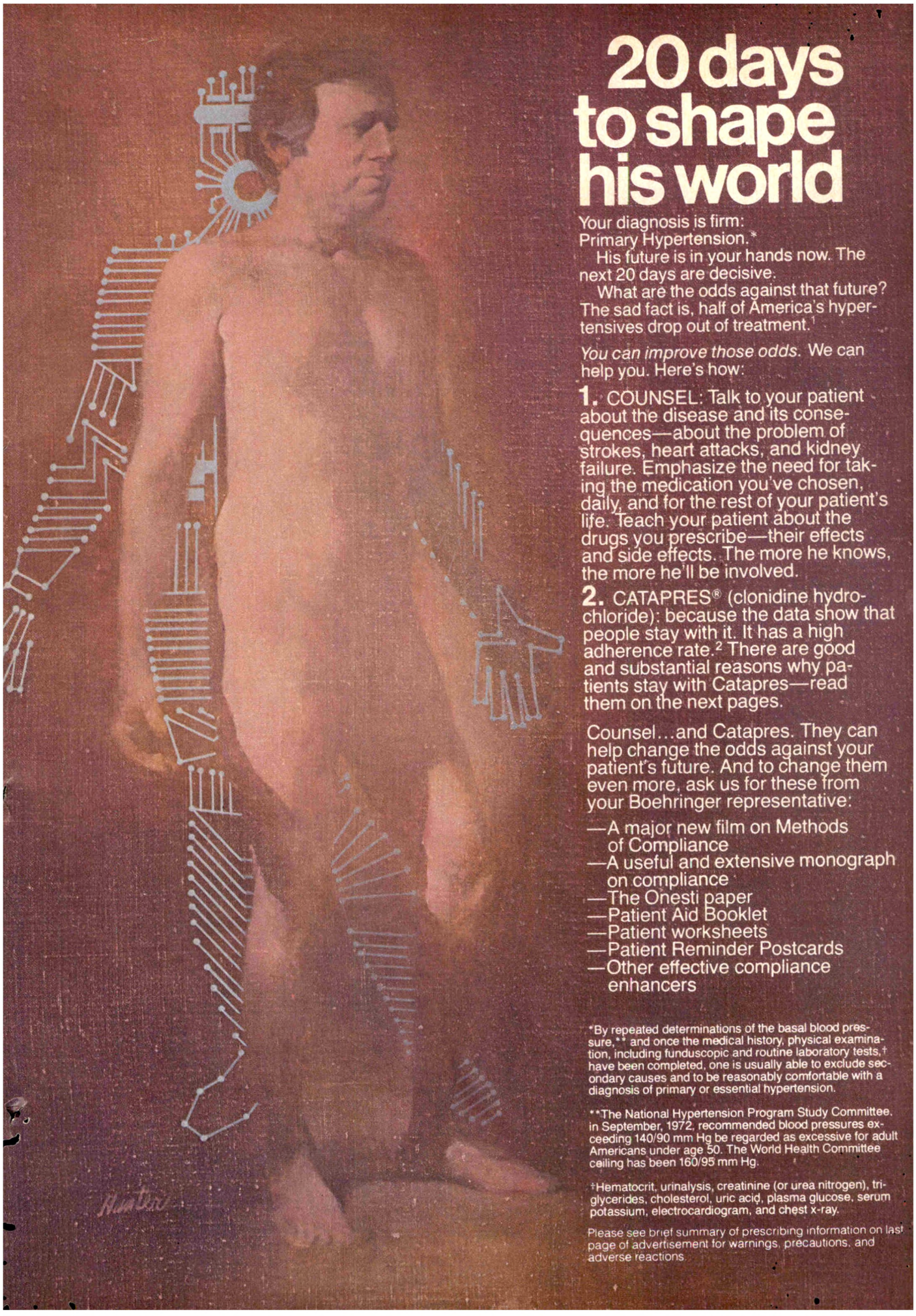
solutions to your clinical problems

. . . consult these books

Visit us at Booth P-7
American Heart Association
Dallas, Texas, Nov. 13–16, 1978

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Washington Square/Philadelphia, Pa./19106



20 days to shape his world

Your diagnosis is firm: Primary Hypertension.*

His future is in your hands now. The next 20 days are decisive.

What are the odds against that future? The sad fact is, half of America's hypertensives drop out of treatment.[1]

You can improve those odds. We can help you. Here's how:

1. COUNSEL: Talk to your patient about the disease and its consequences—about the problem of strokes, heart attacks, and kidney failure. Emphasize the need for taking the medication you've chosen, daily, and for the rest of your patient's life. Teach your patient about the drugs you prescribe—their effects and side effects. The more he knows, the more he'll be involved.

2. CATAPRES® (clonidine hydrochloride): because the data show that people stay with it. It has a high adherence rate.[2] There are good and substantial reasons why patients stay with Catapres—read them on the next pages.

Counsel...and Catapres. They can help change the odds against your patient's future. And to change them even more, ask us for these from your Boehringer representative:

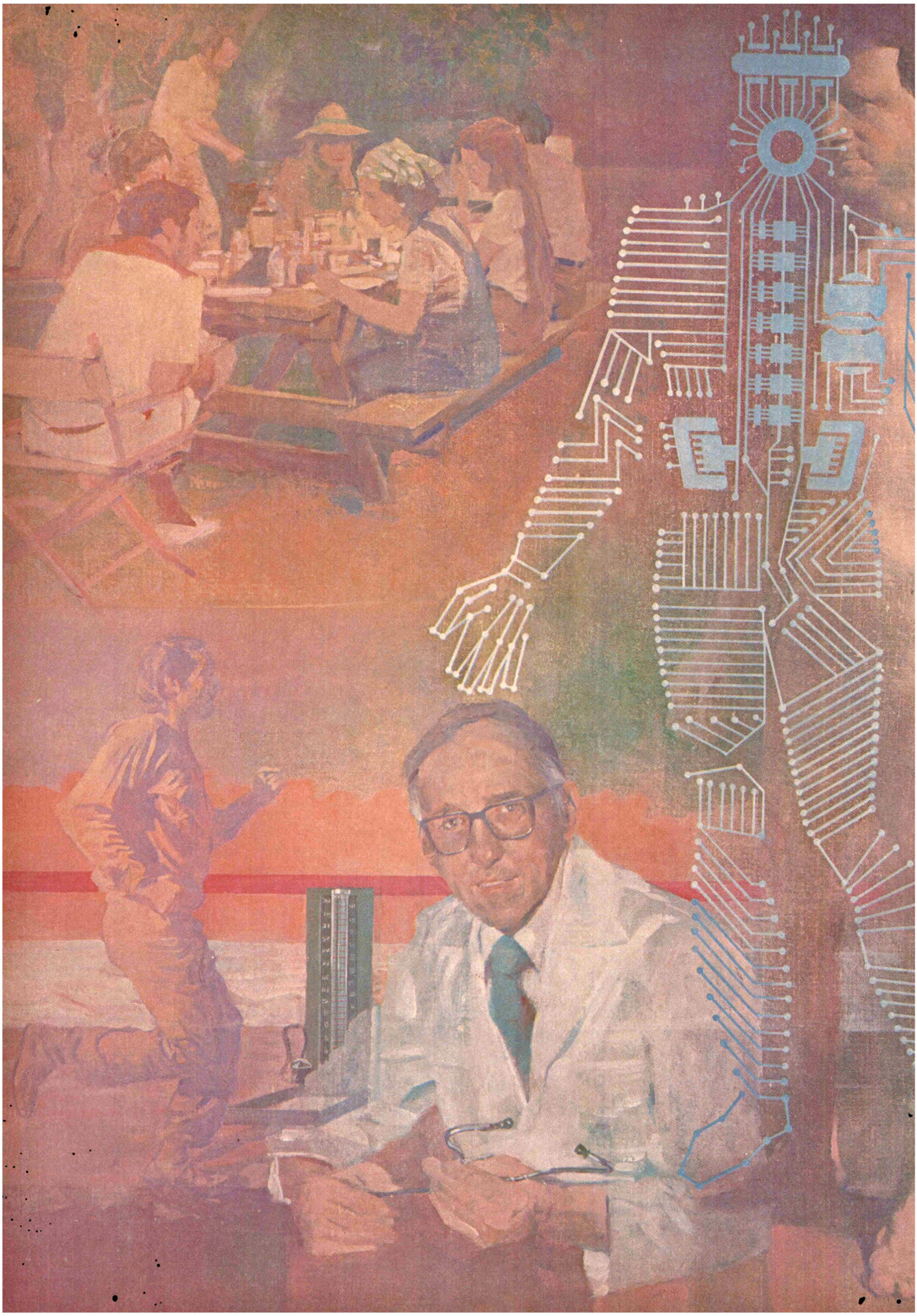
—A major new film on Methods of Compliance
—A useful and extensive monograph on compliance
—The Onesti paper
—Patient Aid Booklet
—Patient worksheets
—Patient Reminder Postcards
—Other effective compliance enhancers

*By repeated determinations of the basal blood pressure,** and once the medical history, physical examination, including funduscopic and routine laboratory tests,† have been completed, one is usually able to exclude secondary causes and to be reasonably comfortable with a diagnosis of primary or essential hypertension.

**The National Hypertension Program Study Committee, in September, 1972, recommended blood pressures exceeding 140/90 mm Hg be regarded as excessive for adult Americans under age 50. The World Health Committee ceiling has been 160/95 mm Hg.

†Hematocrit, urinalysis, creatinine (or urea nitrogen), triglycerides, cholesterol, uric acid, plasma glucose, serum potassium, electrocardiogram, and chest x-ray.

Please see brief summary of prescribing information on last page of advertisement for warnings, precautions, and adverse reactions.





Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl) can help you shape his world

For most hypertensives, you need only two drugs… a diuretic and Catapres.

Start with either, depending on your judgment.

If you've come to expect only this much of Catapres…

1. smooth lowering of blood pressure
2. effective for all degrees of hypertension (mild to moderate in potency)
3. brain, heart, and kidney blood flow preserved

Ask for more of Catapres®

1. no contraindications
2. low incidence of depression and orthostatic hypotension
3. normal hemodynamics
4. no fatal hepatotoxicity
5. excellent record of compliance

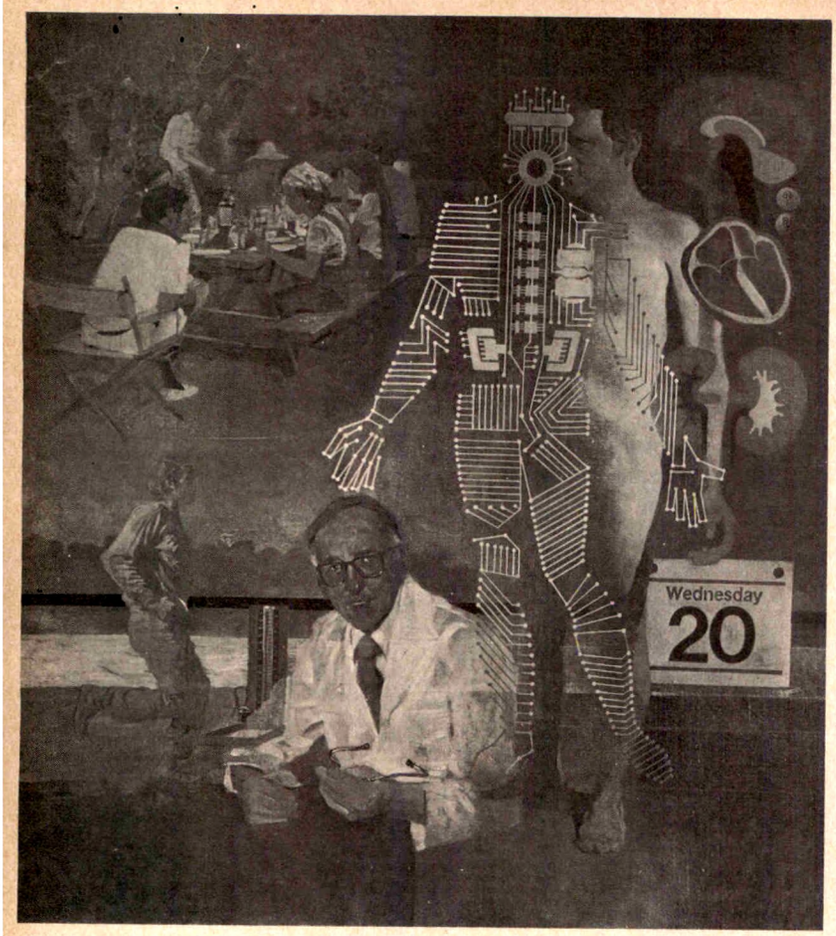
Most common side effects are dry mouth, drowsiness, and sedation, which generally tend to diminish with time.

Please see brief summary of prescribing information on last page of advertisement for warnings, precautions, and adverse reactions.

Tablets of 0.1 and 0.2 mg

Catapres®
(clonidine HCl)

It gives you more than you expect of Catapres



Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl) can help you shape his world

Counsel...and Catapres. They can help change the odds against your patient's future. And to change them even more, ask us for these from your Boehringer representative:

—A major new film on Methods of Compliance
—A useful and extensive monograph on compliance
—The Onesti paper
—Patient Aid Booklet
—Patient worksheets
—Patient Reminder Postcards
—Other effective compliance enhancers

References:
1. Wilber JA, Barrow JS: Am J Med, *52*:653-663, 1972.
2. Data on file at Boehringer Ingelheim Ltd.

Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Ridgefield, CT 06877

Catapres® brand of clonidine hydrochloride
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

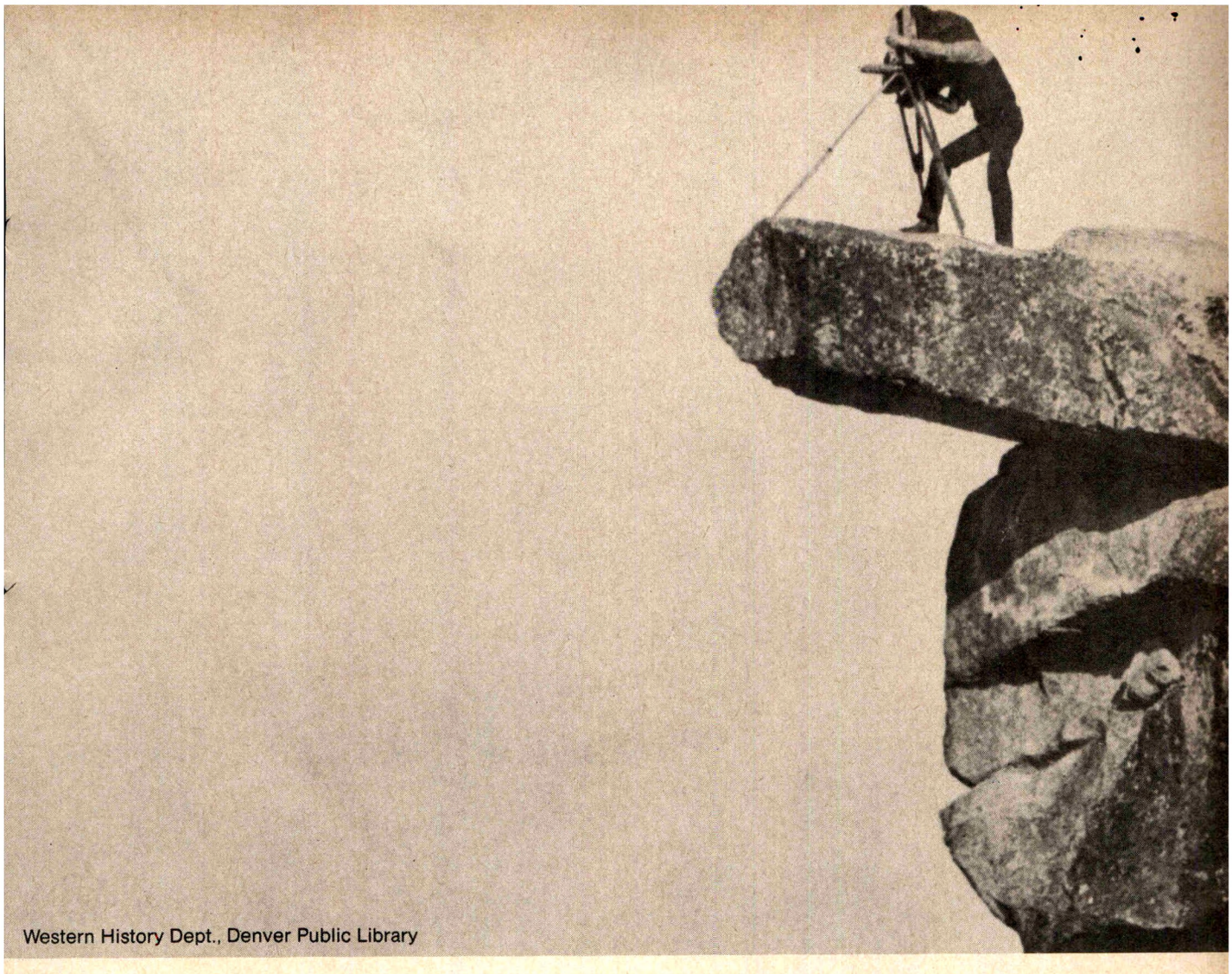
Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

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Ridgefield, CT 06877



Western History Dept., Denver Public Library

When the subject can't be moved, it helps to have a camera that can.

With the introduction of lighter photographic cameras that enabled man to seek new perspectives from which to take pictures, new horizons in realism were made possible.

Searle Radiographics similarly influences technology in the field of nuclear medicine with its extensive line of systems that extend the clinical utility of nuclear cardiology throughout the hospital.

The Pho/Gamma® L.E.M. Low-energy Mobile Scintillation Camera.

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Versatility and great images. They're the reasons why this is the most complete and efficient nuclear cardiology line available. Find out how our product technology can serve your needs in nuclear cardiology by contacting Searle Radiographics.

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SI-8-8429 R1 1007CMO1990

Now is the Age of Arlidin®
(nylidrin HCl)

When peripheral vascular disorders* begin to manifest...



Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).

USV LABORATORIES

USV Laboratories Inc.
Manati, P.R. 00701

it may be time to take these steps



Arlidin (nylidrin HCl)

Arlidin dilates responsive vessels to help increase blood flow in peripheral vascular disorders. At the same time, Arlidin helps maintain mean arterial pressure by providing an increase in cardiac output. The net effect is an increase in oxygen-bearing blood delivered to ischemic tissues, with little risk of hypotensive episodes. Therefore, symptoms of ischemia—intermittent claudication, vertigo and tinnitus, cold hands, cold feet and night leg cramps—may be relieved. And patients feel better.

Walking

The best way to get the PVD patient back on his feet is to get him on his feet. Moderate exercise, such as a therapeutic walking program, helps increase the oxygen uptake by ischemic tissues. By relieving symptoms, Arlidin may help to get the patient back on his feet; walking helps keep him on his feet.

Proper diet

You're the best judge of what your patient should and should not eat. But, particularly for the PVD patient, caffeine should be avoided.

No smoking

The vasoconstrictive action of nicotine, as well as other damaging effects of smoking, should be made clear to the patient with peripheral vascular disease.

The new prescription for PVD*

Walking & Arlidin® (nylidrin HCl)



CARDIOGUARD® 4000 STRESS TEST SYSTEM

We ask questions before any of our instrumentation gets to the drawing board. Because knowing what you need is the most important part of designing what you can use.

Our Cardioguard® 4000 for example. You wanted a system for stress testing and resting ECG your office could use and afford. So the 4000 is compact, mobile, and simple to operate. And with the Exerstress® Display Memory Scope, ST Segment Computer, and our new E-16 Treadmill, you get a complete, automatic 3-channel system for a lot less than you might expect to pay.

The 4000 automatically produces 12-lead ECGs in a letter-size, chart-ready format. With simple push-button controls, you can pre-select any standard lead group, an XYZ lead group, plus your choice of a monitor lead group. And you can change any lead group anytime during the procedure.

The Exerstress Display has a 5-second memory for immediate chart documentation of observed abnormalities. ECG Traces, Elapsed Time, Heart Rate, and the optional ST Level Display all appear on the bright, non-fade, memory scope.

The E-16 Treadmill is our latest. And when coupled with the 4000, the E-16 gives you rugged and reliable performance in speed ranges from 0-10 mph and grades of 0-25 percent, as well as remote control and optional automatic programming.

Like all Del Mar Avionics Systems, the 4000 and E-16 are backed by an extensive service and supply network throughout the country. For more information or a demonstration, write Del Mar Avionics, 1601 Alton Avenue, Irvine, California 92714. Or just call any sales/service office listed below.

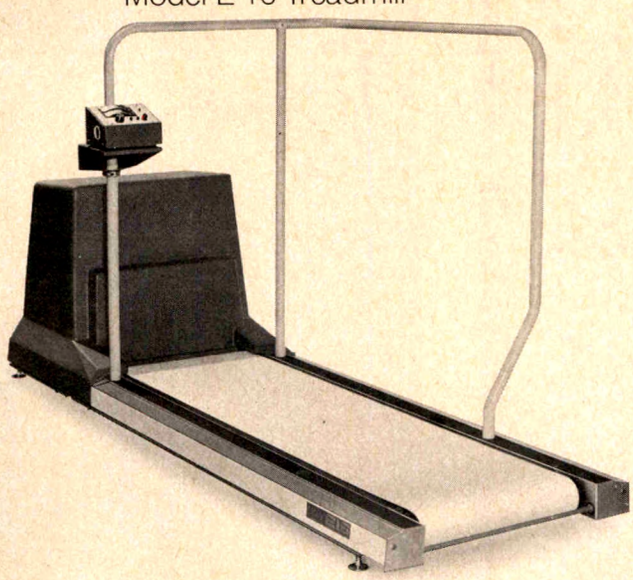
Together, your ideas and our ideas built the 4000 and E-16. An economical, reliable, yet state-of-the-art approach to exercise stress testing.

Which is the very reason we ask questions **before we build answers**

For more information call any one of our Corporate Sales and Service Offices:

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Plus over 60 International Distributors.

Model E-16 Treadmill



DEL MAR AVIONICS

A43

New Horizons in Hyperlipidemia

HIGH BLOOD PRESSURE & ELEVATED LIPIDS: PARTNERS IN PATHOLOGY

Hypertension and hyperlipidemia working in tandem can damage the arterial endothelium—the thin barrier that selectively prevents undue entry of lipids and other blood constituents into the arterial wall. According to the "response-to-injury" hypothesis,[1-3] a break in the endothelium is the first event in a pathologic sequence that can ultimately lead to arterial lesion formation. (See more detailed explanation of this hypothesis in the accompanying schematic illustration at right.)

Endothelial injury: a component of arterial response to hypertension

Animal and human studies[3,4] demonstrate that hypertension can injure the arterial endothelium. The damage seems to be related as much to local hemodynamic stresses at sites of vessel bending or branching[4,5] as to the height of the pressure. It has also been shown that the arterial intima is more permeable to plasma lipoproteins in hypertensive individuals than in normotensives.[6]

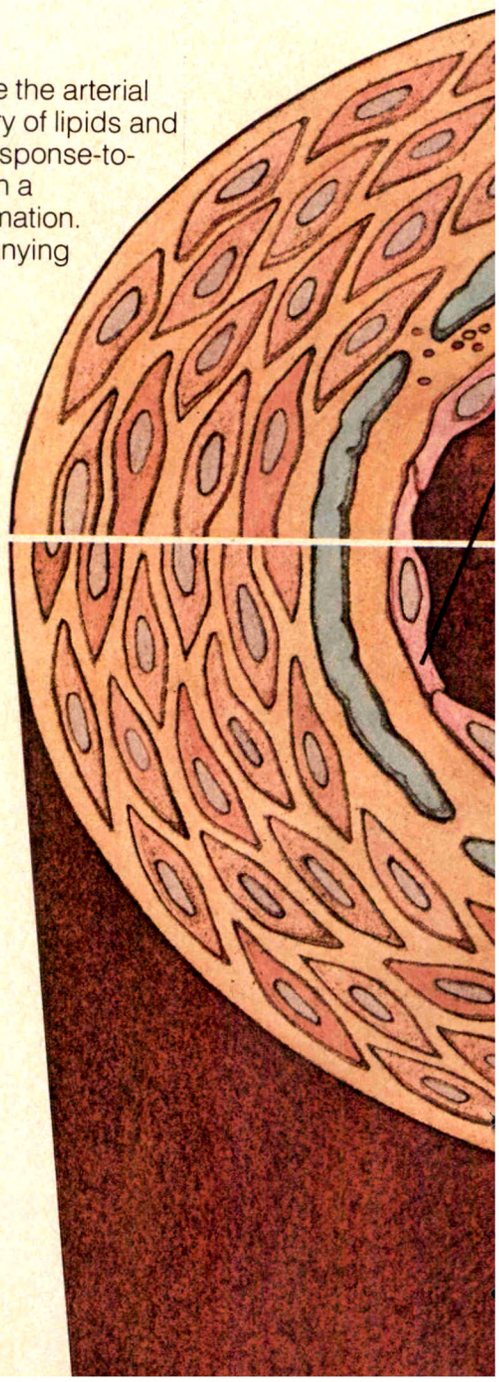
Chronic hyperlipidemia: a factor in initiating and maintaining lesions

In addition to causing lipid deposition in arterial plaques,[5] hyperlipidemia may be an initiating factor in lesion formation.[1] There is also evidence (from primate studies) that elevated serum lipid levels may inhibit the "normal" regression of arterial lesions following a single injury to the endothelium.[1]

1. Ross, R., and Harker, L.: Science *193*:1094 (Sept.) 1976.
2. Ross, R., and Glomset, J. A.: N. Engl. J. Med. *295*:420 (Aug. 19) 1976.
3. Schwartz, S. M.: Cardiovasc. Med. *2*:991 (Oct.) 1977.
4. Glagov, S.: Med. Clin. North Am. *57*:63 (Jan.) 1973.
5. DiGirolamo, M., and Schlant, R. C., in Hurst, J. W., *et al.* (eds.): The Heart, 4th ed., New York, McGraw-Hill, 1978, pp. 1114, 1116.
6. Smith, E. B., and Slater, R. S., in Atherogenesis: Initiating Factors, CIBA Foundation Symposium *12*:39, 1973.

When you find hypertension—look for hyperlipidemia

Ayerst®
Ayerst Laboratories
New York, N.Y. 10017



1

In the normal arterial vessel, the endothelial layer is intact, able to perform its function as partial barrier to the entry of excessive amounts of lipids and other serum constituents into the arterial wall.

2

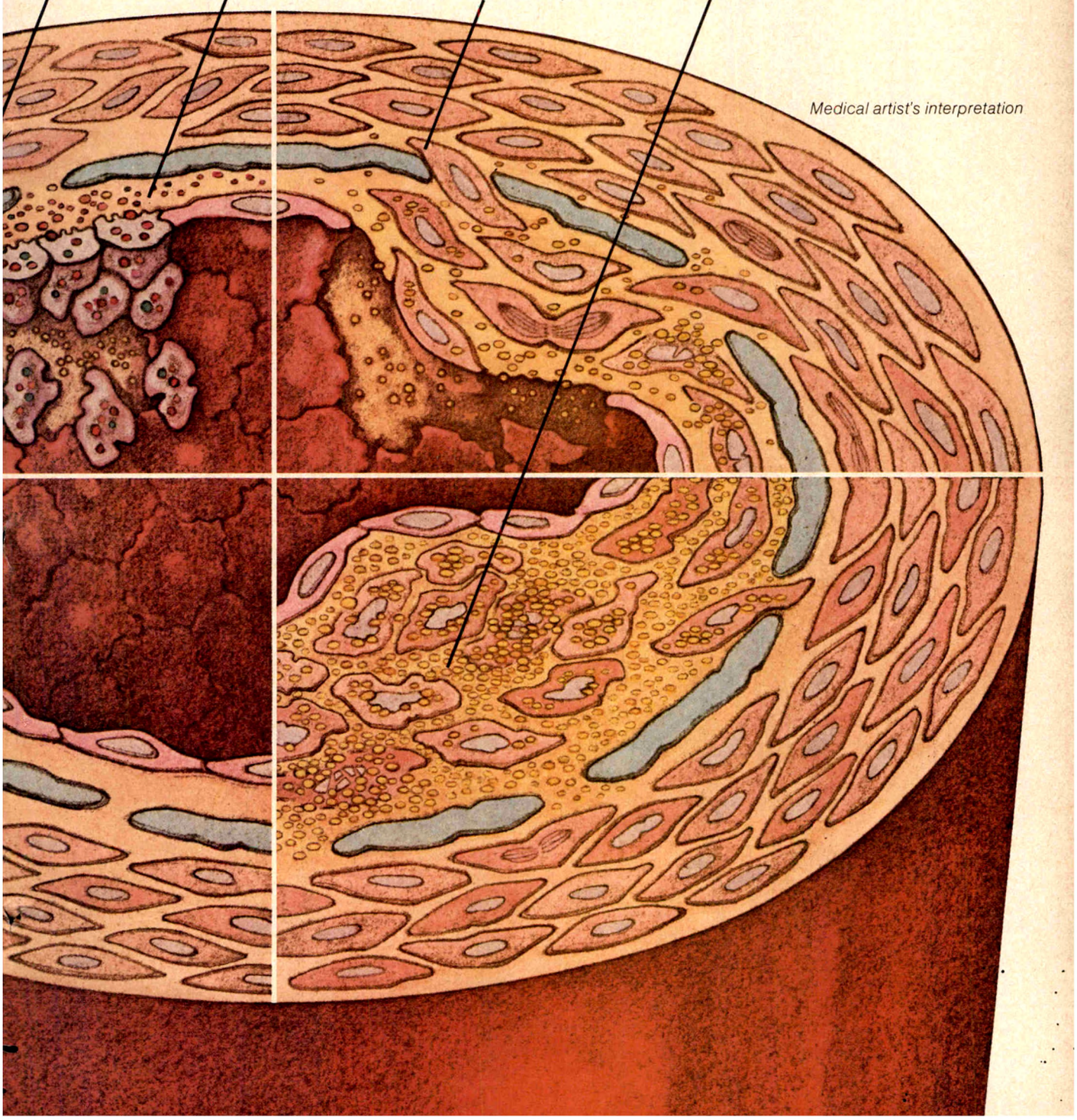
Endothelial injury, resulting from elevated blood pressure and/or high serum lipid concentrations, reduces the effectiveness of this barrier. Serum lipids can then more easily infiltrate subendothelial connective tissue as can factors released from platelet granules after the platelets have adhered to the subendothelial collagen.

3

Smooth muscle cell proliferation is stimulated by platelet mitogenic factors, plasma lipoproteins and other plasma constituents. The cells migrate from the media of the vessel into the intima, where they continue to multiply. Endothelial cells regenerate to cover the exposed intima. Concurrently, in hyperlipidemic individuals, arterial smooth muscle cells are exposed to, and may internalize, large amounts of lipid substances which eventually can cause them to rupture and die.

4

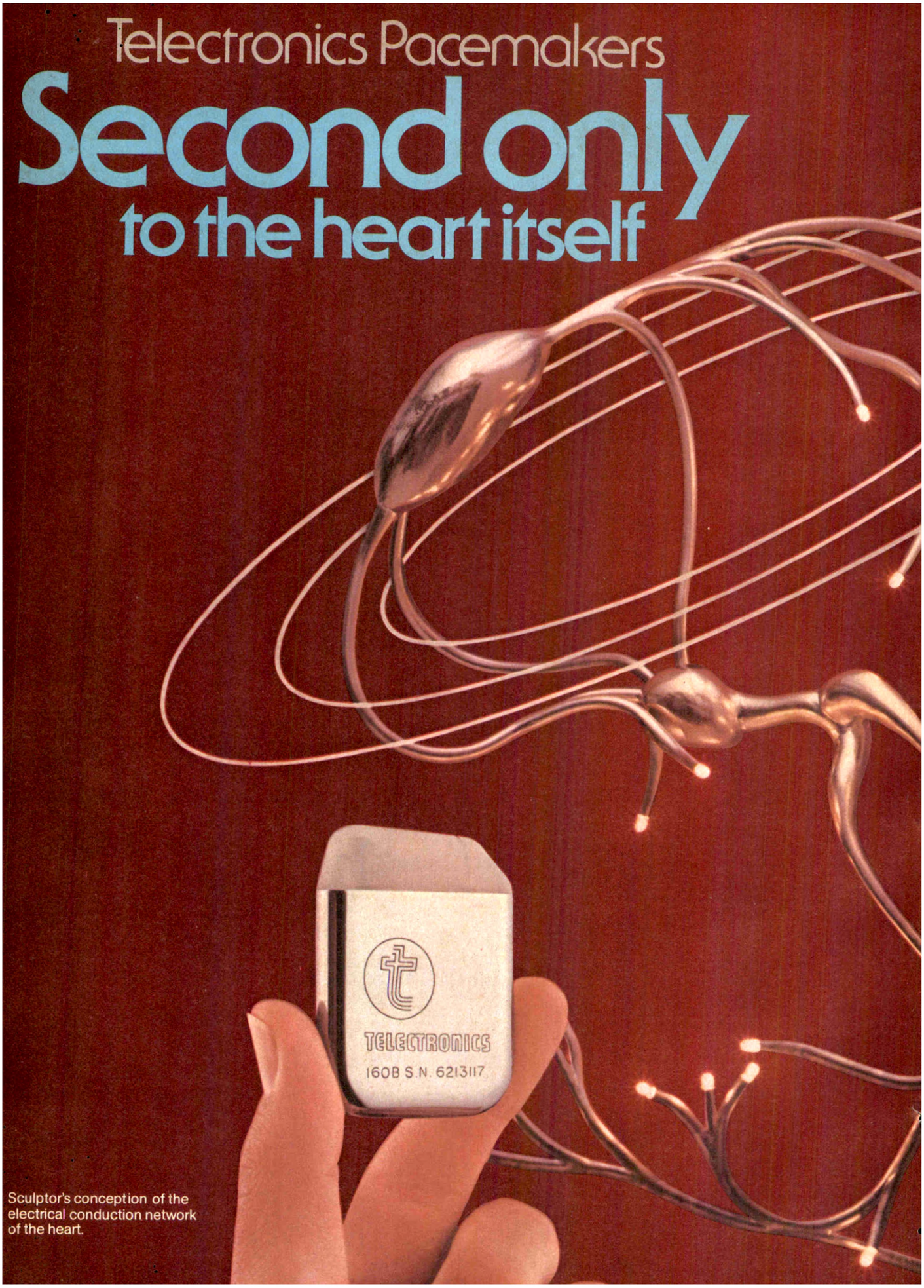
The characteristic arterial lesion shown here is the product of smooth muscle cell proliferation, accumulation of intracellular and extracellular lipids, and debris from muscle cell necrosis. This is the end result of *chronic* or *repeated* endothelial injury. In contrast, the single or widely separated instances of endothelial damage that occur in all persons at varying times usually allow for lesion regression and repair.



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The American Journal of CARDIOLOGY®

VOLUME 42

NUMBER 4

CLINICAL STUDIES

Detection of Critical Coronary Lesions With Treadmill Exercise Testing: Fact or Fiction?

RAFAEL LEVITES, MD, FACC
GARY J. ANDERSON, MD, FACC

Philadelphia, Pennsylvania
Trenton, New Jersey

This study was designed to determine whether treadmill exercise testing could identify patients with critical coronary lesions. Critical lesions were defined as obstruction of the left main coronary artery or concomitant narrowing of the left anterior descending and circumflex coronary arteries proximal to any major branches. The time of onset and degree of S-T segment depression were evaluated in 25 patients with critical lesions and in 50 patients with other types of lesions. S-T segment depression of 2 mm or more was present in 82 percent of patients with left main coronary disease and in 71 percent of patients with left main coronary equivalent lesions (both $P < 0.02$ when compared with 36 percent of patients with other lesions). However, half of the 37 patients with this degree of S-T segment depression had noncritical lesions. Ischemic changes appearing in the first 3 minutes of exercise were seen in 63 percent of patients with left main coronary disease and 35 percent of the patients with left main coronary equivalent lesions ($P < 0.001$ and $P < 0.002$, respectively, when compared with only 6 percent of patients with other lesions). The incidence of triple vessel disease was significantly greater in patients with critical lesions (55 percent in patients with left main coronary disease and 71 percent in those with left main coronary equivalent lesions versus 10 percent in those with other lesions) ($P < 0.01$). S-T segment depression of 2 mm or more is not a good indicator of critical coronary lesions because it has a low level of specificity. Consideration of the time of onset of ischemic changes adds to its usefulness, but it does not permit a definitive diagnosis in individual patients.

Exercise stress testing has become increasingly popular in evaluating patients with chest pain, not only as a means of detecting coronary artery disease, but also as a predictor of coronary events.[1–5] In this context, a direct relation has been shown between the development of myocardial infarction and ensuing sudden death and the magnitude of exercise-induced S-T segment depression.[2,4,5]

Coronary arteriography has provided the documentation of coronary artery disease that the clinician previously lacked and has made it clear that not all patients with coronary artery disease have the same clinical course. Recent studies have reported a poor prognosis for certain patients. These include patients with triple vessel disease[6,7] or critical coronary lesions (lesions of the left main coronary artery,[8–10] for example

From the William Likoff Cardiovascular Institute of the Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania and the Cardiology Section, St. Francis Medical Center, Trenton, New Jersey. Manuscript received July 6, 1977; revised manuscript received April 18, 1978, accepted May 10, 1978.

Address for reprints: Rafael Levites, MD, Cardiology Section, St. Francis Medical Center, 601 Hamilton Avenue, Trenton, New Jersey 08629.

or severe involvement of the left anterior descending and circumflex vessels proximal to any major branches (so-called left main coronary equivalent lesions) particularly in the period immediately after coronary arteriography.[11] Identification of these patients with critical lesions would be most desirable, especially with use of a simple noninvasive method such as exercise testing.

The purpose of our study was to determine whether treadmill exercise testing could identify a subgroup of patients with critical coronary lesions on the basis of a markedly positive exercise test.

Methods

Patients: The study group comprised patients who underwent treadmill exercise testing before coronary arteriography. All studies were performed to evaluate chest pain. We excluded patients without significant coronary artery disease and those who had congenital heart disease, rheumatic valve disease or hypertrophic subaortic stenosis. Of the 210 consecutive patients studied, 86 patients had no significant coronary disease; 49 patients were excluded because of equivocal exercise tests (see later); and 75 patients had adequate treadmill tests and thus constituted the study group.

Treadmill exercise tests: These were performed with patients in the fasting state. Administration of digitalis was discontinued at least 7 days before testing, and that of other medications for at least 3 days. Treadmill tests were performed according to the protocol of Bruce et al.[12] with a single bipolar chest lead in a modified V_5 position. Exercise was continued until 90 percent or more of the predicted maximal heart rate was achieved or until moderate angina pectoris or ischemic changes appeared. In our exercise laboratory, stress testing was terminated within 60 seconds after we noted an ischemic S-T segment response. However, if the patient experienced mild chest pain and the S-T segment remained normal, the exercise test was continued to determine whether S-T segment depression could be induced.

A positive test was defined as horizontal or downsloping S-T segment depression of at least 1 mm for 0.08 second or more after the J point. The study was considered equivocal if the resting electrocardiogram showed ST-T wave changes that precluded an adequate interpretation, if the pattern of left ventricular hypertrophy or left bundle branch block was present or if the patient failed to achieve 90 percent of the predicted maximal heart rate in the absence of S-T segment depression. Treadmill tests were categorized as showing S-T depression of 2 mm or greater, 1 to 1.9 mm or less than 1 mm.

Selective coronary arteriography and left ventriculography: These procedures were performed with the Judkins[13] or Sones technique.[14] Arteriograms were analyzed blindly by independent observers. Critical lesions were defined as obstruction of the left main coronary artery or concomitant narrowing of the left anterior descending and left circumflex coronary arteries proximal to any major branches (that is, so-called left main coronary equivalent lesions). Significant obstruction was defined as 75 percent or greater narrowing in any of the other major vessels.

Patients were classified into three categories according to the presence of critical lesions: Patients with left main coronary disease, patients with left main coronary equivalent disease, and patients with other types of lesions. In addition, patients were grouped, regardless of the presence of critical lesions, according to the number of vessels involved, that is, one, two or three vessel disease. For grouping purposes, a lesion of the left main coronary artery with additional narrowing of the three major vessels was considered three vessel disease. All other left main coronary lesions were considered equivalent to two vessel disease.

Statistical significance was determined using the chi-square method and Student's *t* test for nonpaired data.

Results

General clinical characteristics (Table I): Among the 75 study patients there were 25 with critical lesions, including 11 with left main coronary disease and 14 with left main coronary equivalent lesions and 50 with other types of lesions. Men predominated in the study, and constituted more than 80 percent of patients in all subgroups. The group with critical lesions had a significantly higher mean age and a greater number of patients over 50 years of age. The incidence of previous myocardial infarction was similar among the various groups. All patients had previously complained of chest pain.

Stress testing (Table II): *The duration of exercise* varied markedly among patients in the various

TABLE I

Clinical Characteristics of 75 Study Patients

	Coronary Lesions		
	Left Main Disease	Left Main Equivalent Lesions	Other Lesions
Patients (no.)	11	14	50
Sex			
Male	9 (82%)	13 (93%)	42 (84%)
Female	2 (18%)	1 (7%)	8 (16%)
Age			
Range	40–67	44–67	35–69
Mean ± SEM	55.3 ± 2.7*	54.8 ± 1.8*	49.9 ± 2.5
Over 50 years old	9 (82%)*	10 (72%)	22 (44%)
Chest pain	11 (100%)	14 (100%)	50 (100%)
Previous infarction	4 (36%)	6 (43%)	14 (28%)

* Left main coronary disease or left main equivalent lesions versus other lesions, $P < 0.05$.
SEM = standard error of the mean.

TABLE II

Results of Treadmill Testing

	Coronary Lesions		
	Left Main Disease	Left Main Equivalent Lesions	Other Lesions
Patients (no.)	11	14	50
Test duration (sec)			
Range	60–740	95–780	130–1840
Mean ± SEM	321 ± 56*	399 ± 56*	543 ± 45
Beyond stage III	1 (9%)†	3 (21%)	20 (40%)
Heart rate (beats/min)			
Range	102–169	110–165	112–182
Mean ± SEM	125 ± 6*	137 ± 5	144 ± 3
Heart rate over 140	1 (9%)*	7 (50%)	30 (60%)
Positive test	11 (100%)	14 (100%)	43 (86%)

* Left main coronary disease or left main equivalent lesions versus other lesions, $P < 0.01$.
† Left main disease versus other lesions, $P < 0.02$.
SEM = standard error of the mean.

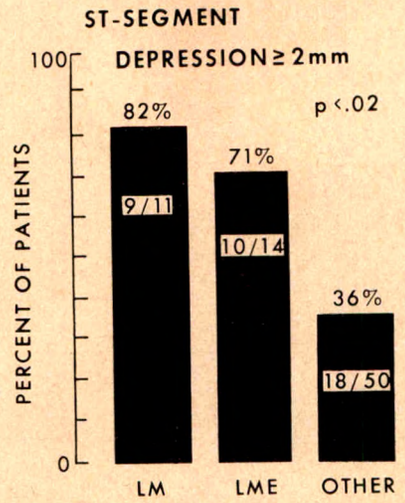


FIGURE 1. Frequency of S-T segment depression of 2 mm or more. There is a significantly greater incidence of marked S-T depression in patients with critical lesions than in patients with other lesions (82 and 71 percent versus 36 percent, both $P < 0.02$). LM = left main coronary disease; LME = left main coronary equivalent lesions; OTHER = other types of lesions. p = probability.

subgroups, but mean exercise duration was significantly lower in patients with critical lesions ($P < 0.01$), and the number of patients exercising beyond stage III was significantly greater among those with noncritical lesions ($P < 0.01$). Mean maximal heart rate was lower in patients with left main coronary disease.

Ischemic S-T changes were seen in all patients (100 percent) with critical lesions and in 43 of 50 patients (86 percent) with noncritical lesions (difference not significant). Exercise-induced S-T-segment depression of 2 mm or more was seen in 9 of 11 patients (82 percent) with left main coronary disease, 10 of 14 patients (71 percent) with left main coronary equivalent lesions and only 18 of 50 patients (36 percent) with other lesions

TABLE III

Distribution of Degree of S-T Segment Depression

S-T Depression (mm)	Coronary Lesions			Total Patients (no.)
	Left Main Disease	Left Main Equivalent Lesions	Other Lesions	
≥2.0	9 (82%)	10 (71%)	18 (36%)	37
1.0–1.9	2 (18%)	4 (29%)	25 (50%)	31
<1.0	0	0	7 (14%)	7
Total	11	14	50	75

(both $P < 0.02$) (Fig. 1, Table III). Moreover, there were significantly more patients with critical lesions in the group with S-T segment depression of 2 mm or more (19 patients) than in the groups with less S-T depression (6 and 0, respectively, both $P < 0.01$). Of the 37 patients with S-T segment depression of 2 mm or more, 19 (51 percent) had critical lesions, whereas 18 (49 percent) had other types of lesions (Table III).

We assessed the ability to predict critical coronary lesions according to the time of onset of ischemic changes (Fig. 2). During stage I of exercise (first 3 minutes), ischemic changes were observed in 63 percent (7 of 11) of patients with left main coronary disease; in 35 percent (5 of 14) of patients with left main coronary equivalent lesions; and in only 6 percent (3 of 50) of patients with other lesions (left main coronary and left main coronary equivalent versus other lesions, respectively, $P < 0.001$ and $P < 0.02$) (Fig. 2, left). Moreover, 80 percent (12 of 15) of patients with ischemic changes during exercise stage I had critical lesions. Of the three patients without critical lesions none had three vessel, one had two vessel and two had one vessel disease. We also observed significant differences between patients with critical and noncritical lesions in the occurrence of ischemic changes during the first 4 minutes of exercise testing (Fig. 2, right). This sign was present in 73

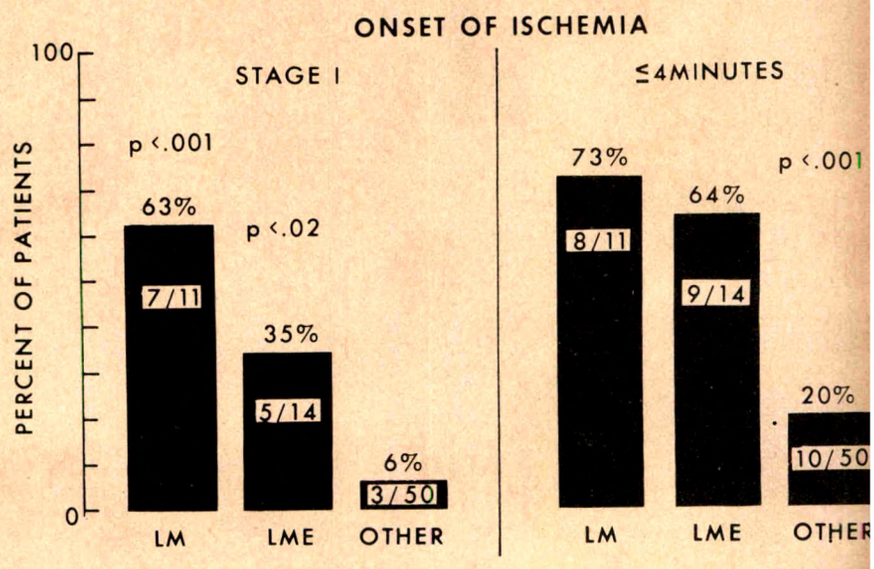


FIGURE 2. Time of appearance of ischemic S-T segment changes. **Left,** the incidence of ischemic changes during stage I of the exercise test was significantly greater in patients with critical lesions than in those with other lesions ($P < 0.001$ and $P < 0.02$ respectively). **Right,** ischemic changes in the first 4 minutes of exercise were significantly greater in patients with critical lesions (73 and 64 percent versus 20 percent, both $P < 0.001$). Abbreviations as in Figure 1.

TABLE IV

Hemodynamic Correlates

	Coronary Lesions		
	Left Main Disease	Left Main Equivalent Lesions	Other Lesions
Patients (no.)	11	14	50
LVEDP (mm Hg)			
Range	6–22	4–35	4–22
Mean ± SEM	12.0 ± 1.4	12.1 ± 2.3	12.8 ± 1.6
LVEDP >14 mm Hg	3 (27%)	3 (22%)	17 (34%)
CI (liters/min per m^2)			
Range	1.4–3.7	2.0–3.5	2.0–3.7
Mean	2.73 ± 0.2	2.76 ± 0.1	2.86 ± 0.2
CI <2.5 liters/min per m^2	5 (46%)	4 (28%)	12 (24%)
LV asynergy	8 (73%)	8 (57%)	33 (66%)

CI = cardiac index; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; SEM = standard error of the mean.

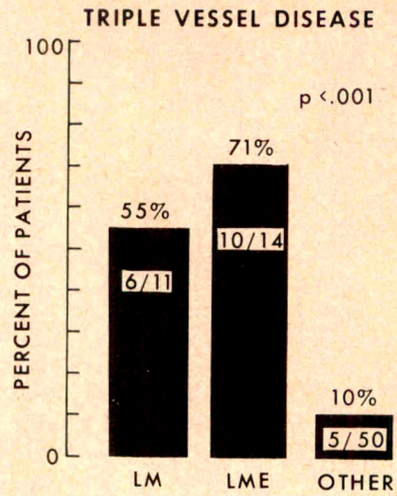


FIGURE 3. Frequency of triple vessel disease. There is a significantly greater incidence of triple vessel disease in patients with critical lesions than in those with other lesions (55 and 71 percent versus 10 percent, both $P < 0.001$). Abbreviations as in Figure 1.

percent (8 of 11) of patients with left main coronary disease; in 64 percent (9 of 14) of patients with left main coronary equivalent lesions; and in only 20 percent (10 of 50) of patients with other lesions (left main coronary and left main coronary equivalent lesions versus other lesions, both $P < 0.001$).

Hemodynamic and angiographic correlates (Table IV): The resting hemodynamics were similar in patients with critical and noncritical lesions. The percent of patients with abnormal hemodynamics and left ventricular asynergy was likewise similar among the various groups of patients.

Of the 11 patients with left main coronary disease, 3 had isolated narrowing of this vessel and 8 had additional involvement of other major vessels; 6 had three vessel, 1 had two vessel and 1 had one vessel disease. All three patients with isolated left main coronary disease had S-T segment depression of 2 mm or more. Ten of 14 patients with left main coronary equivalent lesions had additional disease of the right coronary artery, that is, three vessel disease. Of the four patients with isolated left main coronary equivalent lesions, three had S-T segment depression of 2 mm or more. Of the 50 patients with noncritical lesions, 5 had triple vessel, 17 double vessel and 28 single vessel disease. The incidence of triple vessel disease was significantly greater in patients with critical lesions (Fig. 3).

The degree of S-T segment depression was also correlated with the presence of single, double and triple vessel disease (Table V). Of the 37 patients with S-T segment depression of 2 mm or more, 15 each (41 percent) had two vessel or three vessel disease, and 7 (18 percent) had one vessel disease. The incidence of S-T segment depression of 2 mm or more was significantly greater in patients with double and triple vessel disease than in those with single vessel disease (Fig. 4). Of the 50 patients with noncritical lesions 18 had S-T segment depression of 2 mm or more (Fig. 1); 3 of these had triple vessel, 8 double vessel and only 7 single vessel disease. Of these seven patients with single vessel disease, five patients had involvement of the left coronary system

TABLE V

Degree of S-T Depression and Extent of Coronary Artery Disease

S-T Depression (mm)	Coronary Artery Disease			Total Patients (no.)
	1 Vessel	2 Vessel	3 Vessel	
≥2.0	7 (18%)	15 (41%)	15 (41%)	37
1.0–1.9	16 (52%)	9 (29%)	6 (19%)	31
<1.0	5 (71%)	2 (29%)	0	7
Total	28	26	21	75

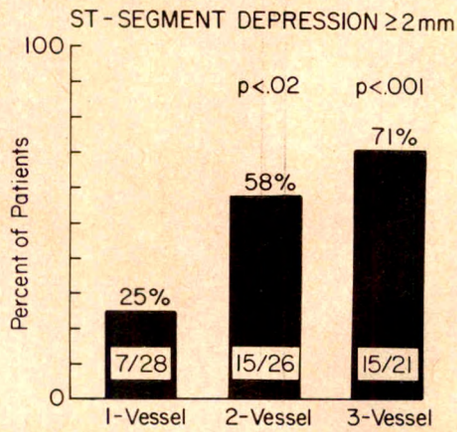


FIGURE 4. S-T segment depression of 2 mm or more and extent of coronary artery disease. The incidence of marked S-T depression was significantly higher in patients with double and triple vessel disease than is those with single vessel disease (71 percent and 58 percent vs 25 percent. $P < 0.001$ and $P < 0.02$, respectively).

and two had isolated narrowing of the right coronary artery. Exercise test results were normal in five patients with single vessel disease and in two patients with double vessel disease. None of the patients with triple vessel disease had normal exercise test results.

Discussion

The role of exercise testing as a noninvasive diagnostic aid in patients with suspected coronary artery disease is now firmly established. Although an ischemic response during stress testing is considered evidence of coronary artery disease, and the interpretation of the test as positive (or negative) has been considered adequate, new observations indicate that quantification of the ischemic response is warranted. The longitudinal studies of Robb and Marks[2] and others[4,5] have demonstrated that the risk of coronary events or sudden death is strikingly greater among patients with marked S-T segment depression during stress testing.

S-T depression equal to or greater than 2 mm and critical coronary lesions: Our report is based on data obtained in a group of patients undergoing treadmill testing and cardiac catheterization to evaluate chest pain. The patient population was highly selective, in that we included only patients who had an adequate treadmill test and had, in addition, angiographic evidence of coronary artery disease. The results of our study are in partial agreement with previous data[15–18] indicating that marked S-T segment depression during exercise testing equal to or greater than 2 mm can identify subgroups of patients with a greater incidence of critical lesions and extensive coronary artery disease. Eighty-two percent of our patients with left main coronary disease and 71 percent of those with left main coronary equivalent lesions demonstrated this degree of S-T segment depression. However, although S-T segment depression of 2 mm or more was a sensitive indicator of critical lesions, it nonetheless had poor specificity: We found the same degree of S-T depression in 36 percent of patients with noncritical lesions, and this latter group of patients comprised 49 percent of the total number of patients with marked S-T segment depression. Cheitlin et al.[17] reported that 25 percent of their patients with S-T segment depression of 2 mm or more had noncritical lesions. However, if one adds their patients who had single proximal obstruction of the left anterior descending artery, a total of 47 percent of their patients had noncritical lesions (as defined in our study), a percent similar to ours. Thus, only one of every two patients with S-T depression of 2 mm or greater can be expected to have a critical lesion.

None of our patients with critical lesions had normal exercise test results. In addition, patients with critical lesions were characterized by a greater mean age, a decrease in mean exercise duration and a lower maximal heart rate.

S-T depression equal to or greater than 2 mm and number of diseased coronary arteries: When our data were analyzed according to the total number of diseased coronary arteries rather than specific patterns of critical or noncritical lesions, a strong relation between marked S-T segment depression and diffuse coronary disease was clear. The incidence of S-T depression of 2 mm or greater was significantly greater in patients with double and triple vessel disease than in those with single vessel disease (58 percent and 71 percent versus 25 percent). In addition, patients with double and triple vessel disease accounted for 82 percent of the tests showing marked S-T segment depression.

S-T depression equal to or greater than 2 mm and incidence of triple vessel disease: Patients with left main coronary disease or left main coronary equivalent lesions had a significantly greater incidence of triple vessel disease. This finding poses an interesting consideration: Is the marked S-T segment depression seen in these patients due to critical lesions or is it dependent on the associated triple vessel disease? In our study, S-T segment depression of 2 mm or more was present in the three patients (100 percent) with isolated left main coronary disease; in three of four patients (75 percent) with left main coronary equivalent lesions without right coronary disease; and in three of five patients (60 percent) with noncritical lesions and triple vessel disease. In the study by Cohen and Gorlin,[18] four of the five patients (80 percent) with isolated left main coronary disease who exercised manifested S-T segment depression of 2 mm or more.

These numbers are too small to warrant definitive conclusions, but it seems that marked S-T segment depression during stress testing is a manifestation of critical lesions independent of the associated diffuse coronary artery disease. So far as we know, no investigation has dealt specifically with this point, probably because isolated left main coronary disease is a rare condition; it was found in only 0.9 percent of 113 patients in the Veterans Administration Cooperative Study.[19]

Time of appearance of ischemic S-T depression: Additional information, such as the time of appearance of ischemic changes, appears to be valuable in evaluating exercise testing.[5,20] Our study showed that most patients (96 percent) with noncritical lesions were able to exercise beyond stage I *before* ischemic changes occurred, whereas significantly more patients with critical lesions manifested ischemic changes during the initia 3 minutes of exercise. Of the patients with ischemi changes during stage I, 80 percent (12 of 15) had critica lesions. A positive test during the initial 4 minutes is als a valuable marker of critical lesions, but although it i more sensitive it is also less specific. However, som patients with critical lesions were able to exercise pas 4 minutes before ischemic changes appeared.

Clinical implications: It is evident from this an other studies that treadmill exercise testing is a usefu noninvasive procedure in the assessment of patient with chest pain, not only to detect coronary artery dis ease, but also to identify subgroups of patients with high incidence rate of diffuse coronary artery disease However, as we have already pointed out, an ischemi S-T segment response of 2 mm or more, with its lo level of specificity, cannot be considered the *onl* marker of critical coronary lesions.

The value of stress testing as a predictor of critical coronary artery disease in these patients can be enhanced by considering *both* marked S-T segment depression and an ischemic response during the first 3 minutes of exercise. However, these changes cannot provide a definitive diagnosis in individual patients.

Acknowledgment

We thank Charles Bemis, MD, Abdulmassih Iskandrian, MD and Demetrios Kimbiris, MD for performing and interpreting the catheterization studies and Edith Schwager for editorial assistance.

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Hemodynamic and Anatomic Determinants of Relative Differences in Amplitude of the Aortic and Pulmonary Components of the Second Heart Sound

PAUL D. STEIN, MD, FACC
HANI N. SABBAH, BS
DANIEL T. ANBE, MD, FACC
FAREED KHAJA, MD, FACC

Detroit, Michigan

Intraarterial sound and pressure in the region of normal semilunar valves and the physical characteristics of the normal semilunar valves were measured to determine the factors that cause a difference in amplitude of the aortic and pulmonary components of the second heart sound. During cardiac catheterization, intraarterial sound was measured near the aortic valve in 15 normotensive patients and near the pulmonary valve in 13 patients with normal pulmonary arterial pressure and 17 patients with pulmonary hypertension. Both the rate of change of the diastolic pressure gradient and the amplitude of the pulmonary component of the second heart sound were higher in patients with pulmonary hypertension than in those with normal pulmonary arterial pressure. In patients with pulmonary hypertension, the amplitude of the pulmonary component of the second sound was as great as that of the aortic component. However, even in patients with pulmonary hypertension, diastolic pressure and the rate of change of the pressure gradient across the valve were lower than on the left side of the heart. These findings suggest that anatomic as well as hemodynamic factors determine the relative amplitude of the pulmonary and aortic components of the second sound. Examination of valves dissected from 12 patients at autopsy revealed that the normal pulmonary valve had a larger surface area and was thinner and more distensible than the normal aortic valve. These observations indicate that both the pulmonary and aortic components of the second sound are related to the rate of change of the diastolic pressure gradient that develops across the valves. However, a comparable driving pressure across the pulmonary valve would cause the pulmonary component of the second sound to have a greater amplitude than the aortic component because of the larger surface area and greater distensibility of this valve. These physical characteristics of the pulmonary valve permit it to produce more compression and thus more sound-pressure than the somewhat smaller and less distensible aortic valve.

A traditional part of cardiac auscultation is determination of the relative intensity of the pulmonary and aortic components of the second heart sound. Experience has taught that the former may exceed the latter in pulmonary hypertension,[1] but some aspects of this phenomenon are not explained by the standard concepts of sound mechanisms. Is the intensity of the sounds strictly a function of diastolic pressure? If so, it is not clear why the pulmonary component of the second sound exceeds the aortic component in patients with pulmonary hypertension because pulmonary diastolic pressure rarely exceeds aortic diastolic pressure in these patients. Is the pulmonary component in fact louder than the aortic component in pulmonary hypertension, or does its relative increase represent a preferential transmission of the pulmonary component to

From the Departments of Medicine and Surgery, Henry Ford Hospital, Detroit, Michigan. This study was supported by Project R38820 from funds supplied by Henry Ford Hospital through a grant from the Ford Foundation, New York, New York. Manuscript received April 3, 1978, accepted May 3, 1978.

Address for reprints: Paul D. Stein, MD, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, Michigan 48202.

TABLE I

Cardiac Diagnoses of 38 Patients Studied

Diagnosis	Patients With Normal Aortic Pressure	Patients With Normal Pulmonary Arterial Pressure	Patients With Pulmonary Hypertension
Normal	3**	2	0
Coronary artery disease	7**	9	1
Mitral stenosis or regurgitation	3**	0	11
Aortic stenosis or regurgitation	0	1	1
Atrial septal defect	1*	1	0
IHSS after repair	1	0	0
Cardiomyopathy	0	0	1
Pulmonary hypertension, cause undetermined	0	0	3

In seven patients sound was measured in the region of both the aortic and the pulmonary valve. * indicates one of these patients, and ** indicates two.
IHSS = idiopathic hypertrophic subaortic stenosis.

the chest wall because the pulmonary valve is closer to the wall of the chest? What are the hemodynamic and anatomic factors that affect the intensity of these two components of the second heart sound? The purpose of this study is to answer some of these questions.

Methods

Studies in patients: Intracardiac sound was measured during diagnostic cardiac catheterization in 38 patients. In 15 of these it was measured just above the aortic valve and in 30 just distal to the pulmonary valve. (In 7 of the 38 it was measured at both the aortic and the pulmonary valves; 2 of these 7 patients had pulmonary hypertension, and 5 had normal pulmonary arterial pressure.) Sound was measured only in the region of a normal aortic or pulmonary valve. Therefore, if a patient had aortic stenosis or insufficiency, only sounds from the right side of the heart were recorded. A valve was considered normal if no pressure gradient was measured across it, no intracardiac diastolic murmur was recorded and no calcium was visualized in the region of the valve during image intensification fluoroscopy. The diagnoses in these patients are shown in Table I. Each of the 15 patients with measurement of the aortic component of the second heart sound had an aortic pressure of less than 140/90 mm Hg, which was defined as normal (Table II). Thirteen of the 30 patients with measurement of the pulmonary component of the second sound had a pulmonary arterial pressure of less than 30/14 mm Hg, which was considered normal.[2] The 17 patients whose pulmonary arterial pressures ranged from 35–90/16–46 mm Hg were considered to have pulmonary hypertension[2] (Table II).

Intracardiac sound and pressure were measured with a Millar Instruments catheter-tip micromanometer and recorded on an Electronics for Medicine VR 6 photographic

TABLE II

Age, Sex, Hemodynamic Measurements and Amplitude of Heart Sounds of 38 Patients*

	Patients With Normal Aortic Pressure (left-sided measurements)	Patients With Normal Pulmonary Pressure (right-sided measurements)	Patients With Pulmonary Hypertension (right-sided measurements)
Pressure (mm Hg)	115/76 ± 3/2 (94–136/63–88)	19/7 ± 2/1 (11–29/3–13)	53/25 ± 5/2 (35–90/16–46)
Maximal negative ventricular dP/dt (mm Hg/sec)	1440 ± 130 (722–2430)	290 ± 40 (140–530)	630 ± 60 (330–1160)
Maximal diastolic d(ΔP)/dt (mm Hg/sec)	1420 ± 110 (830–2200)	240 ± 40 (40–480)	540 ± 60 (240–940)
Sound amplitude (dynes/cm^2)	3000 ± 370 (1210–6060)	770 ± 130 (210–1670)	2850 ± 360 (1400–6820)
Heart rate (beats/min)	78 ± 3 (60–96)	77 ± 4 (56–100)	81 ± 4 (50–104)
Cardiac output (liters/min)	4.8 ± 0.3 (3.1–6.8)	4.9 ± 0.4 (2.7–6.8)	3.8 ± 0.3 (1.4–5.6)
Age (yr)	43 ± 3 (17–54)	45 ± 3 (17–58)	56 ± 2 (41–76)
Sex†	11M, 4F	9M, 4F	11M, 6F

* Values expressed as mean ± standard error of the mean with range in parentheses.
† Number of patients.
d(ΔP)/dt = rate of change of pressure gradient.

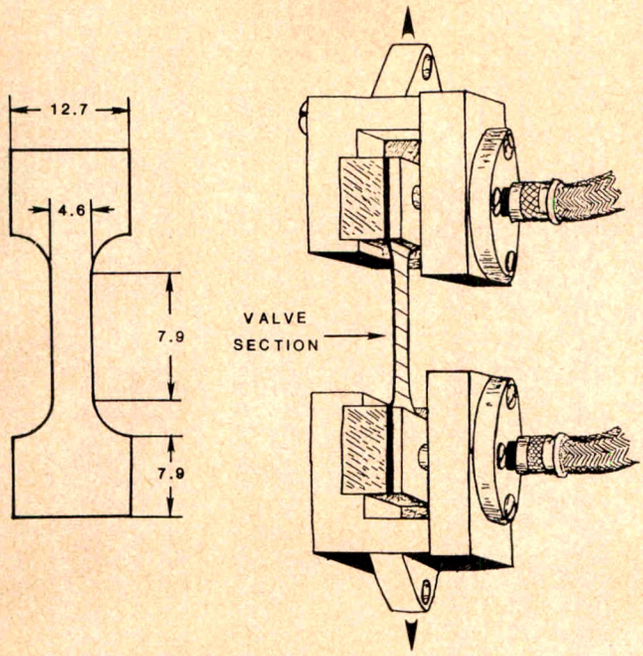


FIGURE 1. Left, diagram of dumbbell-shaped section of the aortic and pulmonary valves that was stamped from the leaflets. Dimensions are shown in millimeters. **Right,** section of the valves held by piston grips in the test device used for measurement of distensibility. (From Mohan and Melvin[5] with permission of the publishers.)

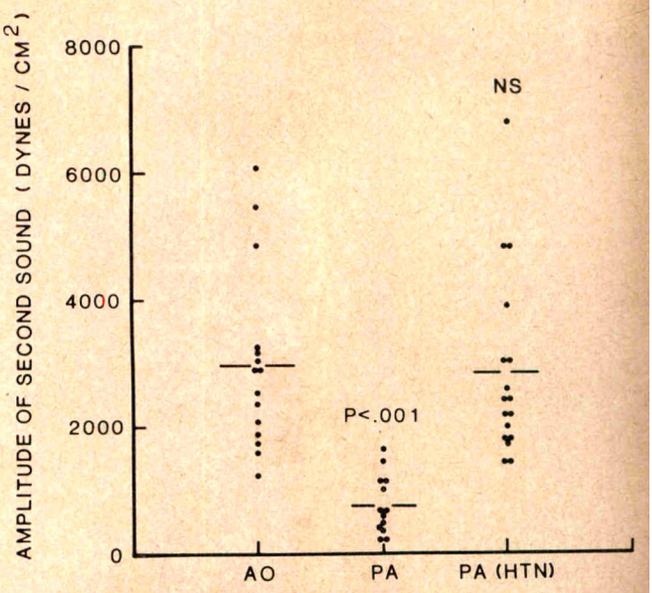


FIGURE 2. Amplitude of the second heart sound, measured intraarterially in the aorta (AO) just above the aortic valve and in the pulmonary artery (PA) in patients with normal pulmonary arterial pressure and patients with pulmonary hypertension (HTN). In patients with normal pulmonary arterial pressure, the amplitude of the pulmonary component of the sound was less than that of the aortic component ($P < 0.001$). In patients with pulmonary hypertension, the two components did not differ significantly (NS). P = probability.

recorder. Intracardiac sound-pressure, referred to as intracardiac sound, was calibrated in dynes/cm^2. The frequency response of the system and the method of calibration of intracardiac sound have previously been described.[3]

The rate at which a difference of pressure developed between the ventricle and aorta (or pulmonary artery) during diastole was termed the rate of change of the diastolic pressure gradient. The rate of development of this pressure gradient across the closed semilunar valve was calculated with the aid of a computer, as described previously.[4]

Physical properties of valves obtained at autopsy: Normal aortic and pulmonary valves were obtained at autopsy from 12 patients (Table II). Patients whose valves appeared deformed or stenotic on gross examination were excluded, as were patients with a clinical history of valvular heart disease. The valve leaflets were dissected free of surrounding tissue and stored in isotonic saline solution at 4° C. The leaflets were weighed on a model H72 balance (Mettler, Heightstown, New Jersey). The surface area of the aortic and pulmonary valve leaflets was measured with planimetry using enlarged photographs of the cusps. The thickness of 11 pairs of valves was

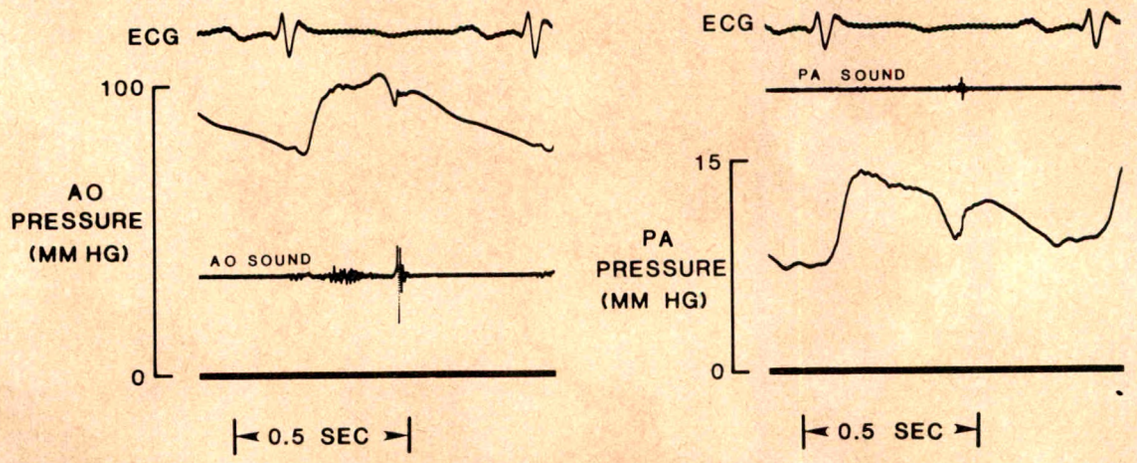


FIGURE 3. Sound and pressure in the aorta (AO) **(left)** and pulmonary artery (PA) **(right)** of a patient with normal pressure. Sound, recorded with the same gain in the pulmonary artery and aorta, was 3,100 dynes/cm^2 near the aortic valve and 870 dynes/cm^2 near the pulmonary valve. ECG = electrocardiogram.

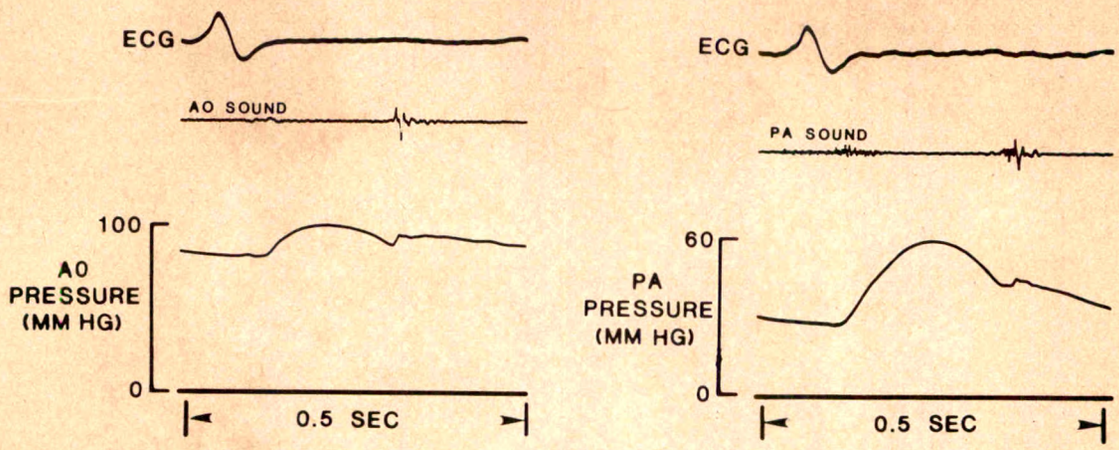


FIGURE 4. Sound and pressure recorded in the aorta (AO) and pulmonary artery (PA) of a patient with pulmonary hypertension. Sound, recorded at the same gain in both the aorta and pulmonary artery, was 1,730 dynes/cm^2 and 1,610 dynes/cm^2, respectively. ECG = electrocardiogram.

measured near the midpoint with the valve unstressed, using a model 5642-1 thickness gauge (Ames, Waltham, Massachusetts).

The extent that the valve tissue stretched with a given load was measured with an Instron TTC Universal testing machine (Canton, Massachusetts) in 10 pairs of valves. Sections of uniform dimensions were cut in a circumferential direction at the free margin of the leaflets by stamping them out with a metal die. Sections of the valve leaflets were gripped by low mass piston grips that produced a constant clamping force while permitting one to observe the thinning of the specimen during deformation.[5] The specimens of the valve that were held between the clamps were 7.9 mm in length and 4.6 mm in width (Fig. 1). The crosshead of the test device was moved at 1.27 cm/sec, causing the tissue to stretch at that rate. The resultant load on the specimen was measured with a piezoelectric load cell (Instron tensile load cell C). Recordings of load and elongation were made on a Honeywell photographic recorder. A load of 8.9×10^4 dynes was arbitrarily selected to compare the distensibility of the aortic and pulmonary valves.

Results

Studies in patients: The amplitude of the pulmonary component of the second heart sound in patients with a normal pulmonary arterial pressure was significantly lower than that of the aortic component in patients with a normal aortic pressure (770 ± 130 versus 3,000 ± 370 dynes/cm^2) (mean ± standard error of the mean) (P <0.001) (Fig. 2 and 3, Table II). In contrast,

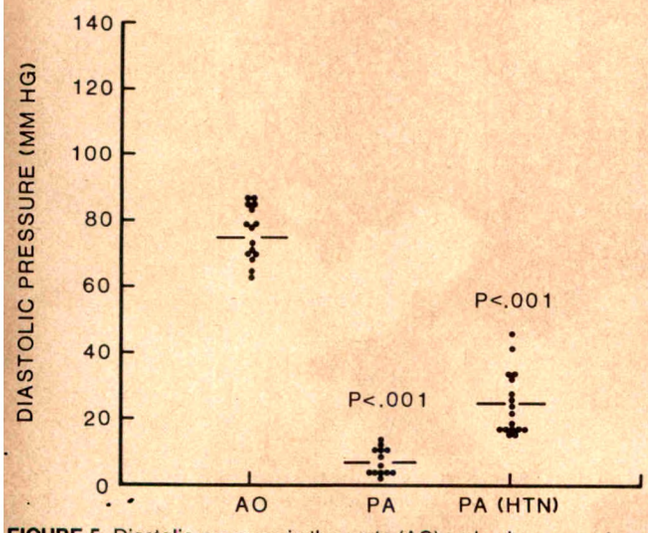


FIGURE 5. Diastolic pressure in the aorta (AO) and pulmonary artery (PA) of patients with a normal pulmonary arterial pressure and pulmonary hypertension (HTN). The pulmonary arterial diastolic pressure was less than aortic diastolic pressure (P [probability] <0.001), even in patients with pulmonary hypertension.

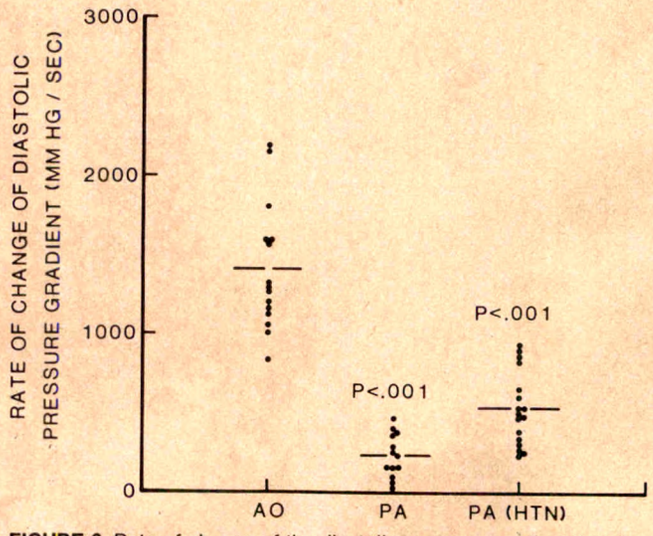


FIGURE 6. Rate of change of the diastolic pressure gradient that developed across the aortic (AO) valve and pulmonary valve in patients with normal pulmonary arterial (PA) pressure and patients with pulmonary hypertension (HTN). The rate of change of the pressure gradient was lower across the pulmonary valve than across the aortic valve (P [probability] <0.001) both in patients with pulmonary arterial hypertension and in patients with normal pulmonary arterial pressure.

in patients with pulmonary hypertension the pulmonary and aortic components were similar in amplitude (2,850 ± 360 versus 3,000 ± 370 dynes/cm^2) (difference not significant) (Fig. 2 and 4), although the pulmonary arterial diastolic pressure (25 ± 2 mm Hg) was lower than the aortic diastolic pressure (76 ± 2 mm Hg) (P <0.001) in these patients (Fig. 5).

The maximal rate of change of the diastolic pressure gradient that developed across the semilunar valves just after valve closure was higher in patients with pulmonary hypertension (540 ± 60 mm Hg/sec) than in patients with normal pulmonary arterial pressure (240 ± 40 mm Hg/sec) (P <0.001). However, even in the patients with pulmonary hypertension the rate of change of the gradient across the closed pulmonary valve was significantly lower than that across the aortic valve (1,420 ± 110 mm Hg/sec) (P <0.001) (Fig. 6).

Physical characteristics of the valve leaflets: The surface area of the aortic valve leaflets measured at autopsy was smaller than that of the pulmonary valve leaflets (8.61 ± 0.58 versus 9.93 ± 0.75 cm^2) (P <0.01) (Table III). The aortic valves, although smaller in surface area, were heavier than the pulmonary valves (0.61 ± 0.04 versus 0.43 ± 0.04 g) (P <0.001), and the average thickness of the aortic leaflets was twice that of the pulmonary valve leaflets (0.31 ± 0.03 versus 0.15 ± 0.03 mm) (P <0.001). When subjected to a load of 8.9 × 10^4 dynes, sections from the aortic valve stretched less than sections from the pulmonary valve (1.31 ± 0.18 versus 2.20 ± 0.27 mm) (P <0.01) (Table III).

TABLE III

Physical Characteristics of Normal Valves Dissected at Autopsy in 12 Cases*

	Aortic Valve	Pulmonary Valve
Surface area (cm^3)	8.61 ± 0.58 (5.74–11.84)	9.93 ± 0.75 (5.60–14.75)
	P <0.01	
Weight (g)	0.61 ± 0.04 (0.34–0.80)	0.43 ± 0.04 (0.21–0.67)
	P <0.001	
Thickness (mm)	0.31 ± 0.03 (0.15–0.48)	0.15 ± 0.03 (0.03–0.36)
	P <0.001	
Distension with 8.9 × 10^4 dynes load (mm)	1.31 ± 0.18 (0.53–2.53)	2.20 ± 0.27 (1.47–4.20)
	P <0.01	

* Values expressed as mean ± standard error of the mean with range in parentheses.
P = probability.

Discussion

Hemodynamic factors determining amplitude of components of second heart sound: In patients with pulmonary hypertension, the average pulmonary component of the second heart sound, measured intraarterially, was as loud as the average aortic component. In many patients with pulmonary hypertension, the pulmonary component exceeded the aortic component of normotensive patients. However, pulmonary arterial diastolic pressure never exceeded aortic diastolic pressure. Previous left-sided cardiac studies in dogs[6,7] and patients[4] established that the amplitude of the second heart sound is related to the rate of change of the diastolic pressure gradient that develops across the closed aortic valve. In this study, we found that the pulmonary component of the second heart sound is also of greater amplitude in patients with an elevated rate of change of the diastolic pressure gradient across the pulmonary valve. Prominent changes in the pulmonary component of the second heart sound occurred, with relatively small increments in the rate of change of the diastolic pressure gradient. Although the rate of change of this gradient increased in patients with pulmonary hypertension, it did not equal the rate of change of the pressure gradient that developed across the aortic valve. Therefore it appears that factors in addition to hemodynamic factors determine the amplitude of the second heart sound.

Anatomic factors determining amplitude of components of second heart sound: Measurements of the normal valves dissected at autopsy revealed that the pulmonary valve is larger in surface area, lighter, thinner and more distensible than the aortic valve. These findings suggest that the pulmonary valve would tend to deflect with a greater velocity than the aortic valve when caused to vibrate by a comparable driving force. We have shown,[8] with high speed motion pictures of a normal porcine aortic valve mounted in a simulated circulatory system, that the rate of center-line deflection of the valve cusp is related to the amplitude of sound. This finding agrees with acoustic theory based on the sound-pressure generated by a vibrating piston in an infinite baffle[9]; it also agrees with the sound-pressure predicted to occur by first order mathematical modeling of the vibrating leaflets.[10] Because the sound-pressure caused by the vibrating semilunar valves is related to the rate at which the valves distend, the thinner and more distensible pulmonary valve is likely to distend at a greater velocity than the aortic valve and therefore to produce more compression and sound-pressure.[11]

The larger surface area of the pulmonary valve would contribute to the relatively greater amplitude of sound produced by the vibrations of the closed pulmonary valve than by those of the aortic valve. The sound-pressure produced by a loudspeaker is comparable, the sound-pressure being greater when there is a larger radiating surface.[9] The sound-pressure produced by the vibrating semilunar valve leaflets, according to preliminary mathematical modeling, would relate to the fourth power of the surface area of the leaflets.[10]

Clinical factors determining valve vibration When considering the amplitude of either component of the second heart sound, one must consider two general determinants of valve vibration: the constitutive characteristics of the valve and the fluid dynamic factors related to valve vibration. The constitutive characteristics of a normal valve include surface area and distensibility. As shown in this study, the pulmonary valve has a larger surface area and is more distensible than the aortic valve and, because of these factors, tends to

produce a greater sound than the aortic valve. Diseases that affect the anatomic structure of the valve also affect the characteristics of its vibration and thus the sound generated. Calcific aortic stenosis causes the valve to become stiff and therefore causes a diminished rate of deflection, resulting in a diminished sound.[12] Regurgitant valves also produce a reduced sound, perhaps because of a reduced ability of the valve to tense properly and to vibrate during early diastole.[3] The principal fluid dynamic factor that affects the amplitude of the second heart sound appears to be the rate of development of the pressure gradient across the valve, which is strongly dependent on the negative rate of change of ventricular pressure. The diminished second heart sound in patients with poor ventricular performance reflects the diminished rate of change of the pressure gradient across the aortic valve, which results from a diminished rate of isovolumic relaxation.[4] The viscosity and density of the blood probably also affect the diastolic vibrations.[10,13]

In summary, our intraarterial measurements revealed that the pulmonary component of the second heart sound may equal or exceed the aortic component in pulmonary hypertension. The relatively greater amplitude of the pulmonary component often recorded at the chest wall in patients with pulmonary hypertension does not necessarily reflect the greater proximity of the pulmonary valve. Both the pulmonary and aortic components of the second heart sound are affected by the rate of change of the pressure gradient that develops across the valve. In pulmonary hypertension the rate of change of the pressure gradient increases, and therefore the pulmonary component of the second heart sound increases. However, the rate of change of the pressure gradient was lower across the pulmonary valve than across the aortic valve. Therefore it appears that factors other than hemodynamic factors interact to permit the pulmonary component to equal or exceed the aortic component of the second heart sound. Our observations suggest that these factors are the surface area of the pulmonary valve and its greater distensibility.

Acknowledgment

Measurements of distensibility and thickness of the valves were made by John W. Melvin, PhD, Head of Biomechanics, Highway Safety Research Institute, University of Michigan, Ann Arbor, Michigan.

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Apparent Reduction of Aortic and Left Heart Chamber Size In Atrial Septal Defect

ANTHONY N. DeMARIA, MD, FACC
LESLIE E. OLIVER, MB
HUGO G. BORGREN, MD, FACC
LILLY GEORGE, MD
DEAN T. MASON, MD, FACC

Davis and Sacramento, California

Although it is widely held that the size of the aorta and left atrium is diminished in patients with atrial septal defect, few data are available to support this contention. Therefore, aortic and left heart chamber dimensions in 24 patients with documentation of an atrial septal defect at cardiac catheterization were compared with those of 22 normal persons. The data were obtained using echocardiography, cineangiography and qualitative estimation of aortic size from chest X-ray films. Aortic size was similar in the patients with an atrial septal defect and normal subjects (1.7 cm/m^2 for both groups on angiography). Although the aortic diameter was estimated to be small in 12 of the 24 patients with an atrial defect on chest X-ray films, no difference existed in aortic measurements on echocardiography or angiography in patients judged to have normal as opposed to those judged to have reduced aortic size. Although the left atrial echographic dimension tended to be slightly greater in the patient group than in normal subjects (2.2 versus 1.9 cm/m^2), this difference was not statistically significant. The echographic ratio of left atrial to aortic size was greater in the patient group (1.3 versus 1.1) ($P < 0.02$). Stroke index was similar in the two groups (37.5 versus 42.8 ml/m^2 with the dye-dilution technique and 35.1 versus 36.3 ml/m^2 on angiography). Although echocardiographic left ventricular diastolic dimension was slightly smaller in the patient group than in normal subjects (2.5 versus 3.0 cm/m^2) ($P < 0.02$), diastolic volume index on angiography was similar in the two groups (50.1 versus 52.9 ml/m^2). Thus, these data do not support the conventional belief that, because of a reduced stroke volume, the size of the aorta and left atrium is diminished in patients with an atrial septal defect.

From the Section of Cardiovascular Medicine, Departments of Medicine, Physiology and Radiology, University of California at Davis, School of Medicine and Sacramento Medical Center, Davis and Sacramento, California. This study was supported in part by Research Program Project Grant HL 14780 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland and Research Grants from the Golden Empire Chapter of the American Heart Association, Sacramento, California. Dr. Oliver is the recipient of the Overseas Research Teaching Grant of the National Heart Foundation of Australia, Melbourne, Australia. Manuscript received February 13, 1978; revised manuscript received May 24, 1978, accepted May 24, 1978.

Address for reprints: Anthony N. DeMaria, MD, Section of Cardiovascular Medicine, University of California, School of Medicine, Davis, California 95616.

It is a traditional belief[1–10] that atrial septal defect is associated with a small aorta, a normal or a small left atrium and a left ventricle of diminished dimension. This view is largely based on the radiologic finding of an aortic silhouette that appears small on chest X-ray films and the assumption that a left to right shunt at the atrial level should produce underfilling of the left ventricle and consequently a diminished stroke volume and cardiac output.

Despite the almost universal acceptance of the proposition that aortic, left atrial and left ventricular size is reduced in patients with atrial septal defect, few data are available to support this concept. Indeed, in our hospital we frequently encountered patients with an atrial septal defect without such findings; this absence was thus misleading from a diagnostic standpoint. Therefore, in this study we compared aortic root and left heart chamber size in patients with an atrial septal defect and in normal subjects using echocardiography and cineangiography.

Methods

Patients: Twenty-four patients with an atrial septal defect were studied. These patients, 20 female and 4 male, ranged in age from 4 to 62 years (mean

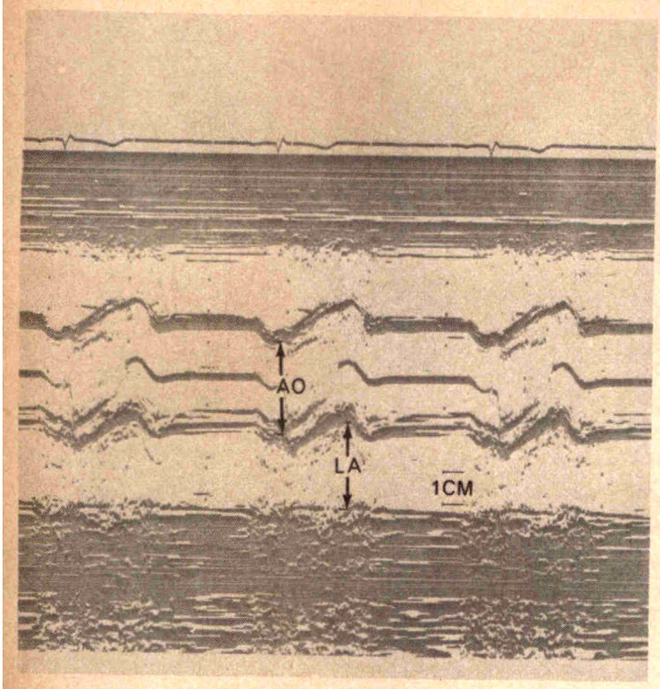


FIGURE 1. Echocardiogram through the plane of the aorta (AO) and left atrium (LA) of a normal subject, depicting the method of measuring these structures. The aorta was measured in an area where the aortic valve leaflets could be well visualized.

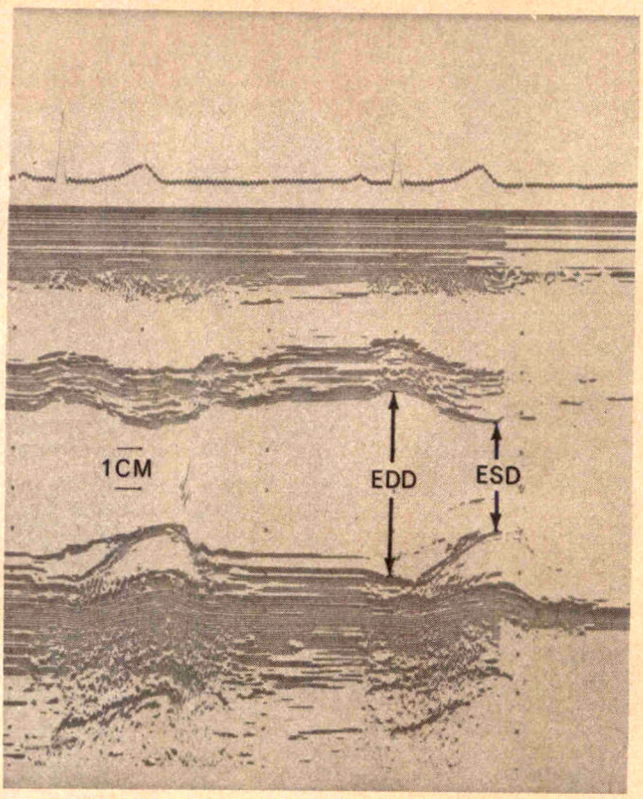


FIGURE 2. M mode echocardiogram through the body of the left ventricle of a normal subject, illustrating the method of measuring this structure. EDD = end-diastolic dimension; ESD = end-systolic dimension.

28). Cardiac catheterization revealed an ostium secundum defect in 22 patients and an ostium primum defect in the remaining 2. No patient with an atrial septal defect had a balanced or predominant right to left shunt, mitral regurgitation or other associated cardiac abnormality. The mean ratio of pulmonary to systemic flow for the group as assessed with oximetry was 2.8 to 1 (range 1.4 to 1 to 5.0 to 1).

Control subjects: Twenty-two normal subjects served as the control group. These subjects, 14 female and 8 male, ranged in age from 4 to 60 years (mean 33). In the course of evaluation for atypical chest pain, 14 of these subjects had had right and left heart catheterization that revealed no abnormalities; the remaining 8 subjects were children of school age, selected for age-matching, whose history, physical examination, electrocardiogram and chest X-ray film were all within normal limits.

Cardiac catheterization: In those patients undergoing this procedure, cardiac output was measured by the indicator dilution method consisting of a 3 ml (3.75 mg) injection of indocyanine green into the left ventricle with subsequent sampling of blood from the brachial artery. Pulmonary and systemic flow data were calculated with oximetry, performed in duplicate, with samples being drawn from the superior and inferior venae cavae; the high, mid and low right atrium; right ventricular inflow, body and outflow areas; and pulmonary and brachial arteries. Biplane left ventricular cineangiography was performed by injecting 0.75 to 1 cc/kg of Hypaque 75® (Winthrop) into either the left ventricle or the left atrium, using 35 mm film at 64 frames/sec and a Phillip's image intensification system with 9 inch (22.8 cm) magnification. Ventricular premature complexes and postectopic complexes were excluded from analysis.

Ventricular volumes were calculated using the single plane, area-length method of Sandler and Dodge,[11] and the aortic root was measured at the junction of the aortic sinuses and ascending aorta at end-diastole in the right anterior oblique projection after the cineangiograms were corrected for magnification by means of a 1 cm grid. On occasion it may be difficult to measure aortic root size in the right anterior oblique projection because of superimposition upon the descending aorta. In such cases, the initial beat opacifying the aortic root that enabled delineation of this structure from the descending aorta was utilized. Thereby, we were able to record aortic measurements with angiography in the same plane used with echocardiography. The coronary angiograms were normal in all patients whose films were obtained.

Echocardiography: M mode echocardiograms were obtained utilizing a commercially available echocardiograph (Ekoline-20A, Smith Kline Instruments) interfaced to either a photographic (model DR8, Electronics for Medicine) or fiberoptic (model 1856, Honeywell Corporation) recorder. Echocardiograms were obtained in the standard manner, generally a day before cardiac catheterization. The following measurements were made from the echocardiogram recorded: The aortic root was measured from the leading edge of the anterior aortic wall to the leading edge of the posterior aortic wall through the plane of the aortic leaflets at end-diastole; the left atrium was measured from the leading edge of the posterior aortic wall echo to the first strong ultrasonic signal from the left atrial posterior wall at peak anterior aortic wall motion during ventricular systole; and left ventricular end-diastolic and end-systolic dimensions were measured from the endocardial surfaces of the interventricular septum and

TABLE I

Comparison of Echographic and Cardiac Catheterization Data in Patients With an Atrial Septal Defect and Normal Subjects

	Aortic Root		Left Atrium:	LA/Ao	LV Size (diastolic):	LV	LV Size (end-diastolic):	Stroke Volume		
	Echo (cm/m^2)	Angio (cm/m^2)	Echo (cm/m^2)	Ratio: Echo	Echo (cm/m^2)	Fractional Shortening	Angio (ml/m^2)	Angio (ml/m^2)	Dye-Dil (ml/m^2)	Qp/Qs
ASD										
Mean	1.66	1.56	2.15	1.30	2.51	34.4	50.10	35.1	37.5	2.8:7
SEM	0.06	0.05	0.13	0.06	0.13	1.63	8.10	5.90	2.18	0.24
Normal	22	14	22	22	22	22	14	14	14	14
Mean	1.68	1.52	1.86	1.10	3.03	35.7	62.86	36.3	42.8	1:1
SEM	0.06	0.06	0.08	0.04	0.14	0.97	3.83	3.16	2.52	—
P value*	NS	NS	<0.06	<0.02	<0.02	NS	NS	NS	NS	<0.001

* Patients with atrial septal defect versus normal subjects.

Angio = cineangiographic dimensions; ASD = atrial septal defect; Dye-Dil = dye-dilution technique; Echo = echocardiographic dimensions; LA/Ao Ratio = ratio of left atrial size at end-systole to aortic root dimension at end-diastole; LV = left ventricular; NS = not significant; *P* = probability; QP/QS = ratio of pulmonary to sytemic flow; SEM = standard error of the mean.

posterobasal left ventricular wall at the peak of the R wave, and at the point of maximal approximation of these structures, respectively (Fig. 1 and 2). All echo values reported represent the mean of 3 beats measured by two observers.

Chest roentgenography: Erect posteroanterior and left lateral chest X-ray films were obtained in all patients and control subjects. These films were subsequently evaluated by a cardiovascular radiologist (H.G.B.) without prior knowledge of the clinical findings, and an assessment of aortic size was recorded. The data were subjected to statistical analysis by Student's *t* test for group data.

Results

Technically adequate echocardiograms and cineangiograms were obtained in all patients and control subjects. The results are summarized in Table I. Data have been corrected for body surface area in regard to all measurements. Because the ratio between female and male subjects was greater in the patients with an atrial septal defect than in the normal group, the data from female and male subjects were separately compared in the two groups. Because no differences were observed in this comparison, the data for both sexes are presented together.

Aortic size: Measurement of aortic size was obtained with both echocardiography and cineangiography, and regression analysis comparing the measurements obtained with both techniques demonstrated close correlation with a correlation coefficient of $r = 0.87$, $P < 0.001$. No difference was observed in the size of the ascending aorta, determined with either angiography or echocardiography, in the patient and normal groups (Fig. 3). Thus, the aortic root measured 1.7 ± 0.06 cm/m^2 (mean ± standard error of the mean for the group) in patients with an atrial septal defect compared with 1.7 ± 0.06 cm/m^2 in normal subjects. The respec-

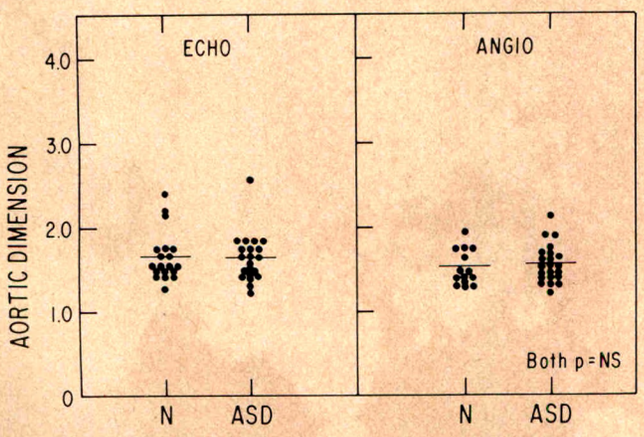


FIGURE 3. Individual value for aortic size (cm/m^2) determined with echocardiography (ECHO) and cineangiography (ANGIO) in patients with an atrial septal defect (ASD) and normal subjects (N). The **horizontal lines** indicate the mean value for each group of patients. NS = not significant; p = probability.

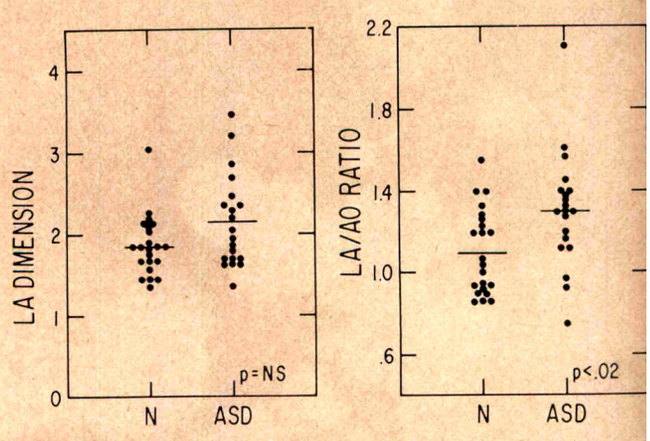


FIGURE 4. Individual values for left atrial (LA) size (cm/m^2) and left atrial to aortic (LA/AO) ratio determined with echocardiography in patients with an atrial septal defect (ASD) and normal subjects (N). The **horizontal lines** indicate the mean values for each group. Abbreviations as in Figure 3.

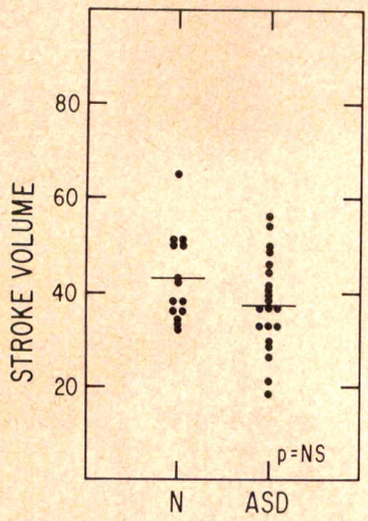


FIGURE 5. Individual values for stroke volume determined with the dye-dilution technique in patients with an atrial septal defect (ASD) and normal subjects (N). The **horizontal lines** indicate the mean values for each group. Abbreviations as in Figure 3.

tive values for aortic dimension on cineangiography were 1.6 ± 0.05 and 1.5 ± 0.08 cm/m^2. The chest X-ray film suggested a diminished aortic root in 12 of 24 patients with an atrial septal defect. However, no difference was observed in aortic root dimension determined with either angiography or echocardiography when these 12 patients were compared with those whose chest X-ray film suggested a normal-sized aorta.

Left atrial dimension: Although the mean value for left atrial size obtained from the echocardiogram was greater in patients with an atrial septal defect than in normal subjects (2.2 ± 0.13 cm/m^2 versus 1.9 ± 0.08 cm/m^2), this difference did not reach statistical significance (Fig. 4). However, the ratio of left atrial to aortic root dimension as obtained by ultrasound was clearly greater in the patient group than in normal subjects. Thus, the ratio of the left atrium to the aorta was 1.30 ± 0.06 in patients with an atrial septal defect compared with 1.10 ± 0.04 in normal subjects (P <0.02).

Left ventricular dimensions and stroke volume: No difference was observed in this study in angiographic left ventricular end-diastolic volume index between patients with an atrial septal defect (50.1 ± 8.0 ml/m^2) and normal subjects (52.9 ± 3.8 ml/m^2). However, by echocardiography left ventricular end-diastolic diameter was slightly smaller in the patient group (2.5 ± 0.13 cm/m^2) than in normal subjects (3.0 ± 0.14 cm/m^2) (P <0.02). There were no significant differences (Fig. 5) between the two groups in left ventricular stroke volume index, as determined with cineangiography (35.1 ± 5.9 and 36.3 ± 0.04 ml/ml^2) in the patient and the normal group, respectively, and dye-dilution studies (37.5 ± 2.2 and 42.8 ± 2.5 ml/m^2 in the respective groups). In addition, shortening fraction of the left ventricle as measured with echocardiography was similar (P <0.05) in the patients (34.4 ± 1.6) and the normal (35.7 ± 0.9) group.

Discussion

It has become a well entrenched clinical axiom that the aorta, left atrium and left ventricle are reduced in size in patients with an atrial septal defect. Thus, descriptions of a small inconspicuous aortic silhouette or diminished left atrial and left ventricular prominence in the setting of an atrial septal defect abound in both the radiologic as well as the cardiologic literature.[1–10] Further, it has been reasoned that these anatomic findings represent the inevitable sequel of a diminished systemic cardiac output secondary to left to right shunting in atrial septal defect, and might well be indicative of a generalized underdevelopment of the left ventricular outflow tract associated with a chronically underfilled left ventricle. Our results clearly demonstrate that the aorta, left atrium and left ventricle are normal in size or even increased rather than decreased in patients with an atrial septal defect.

Alleged diminution in size of aorta: The cardiovascular alteration involving the systemic circulation that has received perhaps the greatest attention in patients with an atrial septal defect has been an alleged diminution in the size of the aorta. Thus, a small or inconspicuous appearance of the thoracic aorta on chest X-ray film has been variously reported in 25 to 75 percent of patients with an atrial septal defect.[1–10] However, in our study the cineangiographic and echocardiographic measurements of aortic diameter in such patients was similar to that observed in normal subjects, a finding in agreement with previous angiographic observations in children with an atrial septal defect.[12] Further, although the appearance of the thoracic aorta on X-ray examination was judged to be diminished in 12 of our 24 patients with an atrial septal defect, ultrasonic and cineangiographic measurements did not substantiate any difference in the caliber of the aorta in these patients and the remaining 12 patients judged to have a normal aortic silhouette. Accordingly, factors other than a decrement of aortic diameter must be sought to explain the abnormal appearance of this structure in patients who have an atrial septal defect. In this regard, previous studies have speculated that the aortic knob may be obscured by an enlarged main pulmonary artery[13] or, alternatively, that the ascending aorta may be displaced into the shadow of the vertebral column by virtue of assuming a more posteroanterior orientation as a result of levorotation from right ventricular enlargement[14,15] in patients with an atrial septal defect. In any event, our findings clearly document that no absolute reduction in aortic diameter exists in patients with an atrial septal defect as compared with normal subjects.

Alleged reduced left atrial size: A reduction in the dimension of the left atrium has also been associated with atrial septal defect and has been used as a differential point in distinguishing left to right shunts due to defects in the atrial septum from those in the interventricular septum or secondary to a patent ductus arteriosus. Thus, it has been assumed that a substantial portion of the blood shunted from left to right by way of the atrial septal defect flows virtually directly from

the pulmonary veins across the septal defect and into the right atrium. However, our data document that the left atrium is not smaller in patients with an atrial septal defect than in normal subjects. Indeed, the left atrial dimension tended to be somewhat greater in our patient group than in the control cohort; however, this difference did not reach statistical significance. Further, when left atrial size was expressed in relation to aortic diameter, this ratio was significantly larger in the patient group than in normal subjects. Thus, it would appear that the left atrium bears at least some volume overload in patients with an atrial septal defect, as it does in patients with a ventricular septal defect and of patent ductus arteriosus. However, in patients with the latter two defects the left atrium is subjected to a pressure overload as well and is thus larger than in patients with an atrial septal defect at similar left to right shunt ratios.

Alleged underfilling of the left ventricle: A small left ventricle in patients with an atrial septal defect was thought to be a logical consequence of the diversion of pulmonary venous blood from the left to the right atrium. In our study, measurements of left ventricular end-diastolic dimension by ultrasound were smaller in the patient group than in normal subjects, a finding consistent with the recent work of Wanderman et al.[16] However, measurements of left ventricular volume obtained from left ventricular cineangiograms in the right anterior oblique projection were similar in the two groups. It is most probable that the apparent disparity between echocardiographic and angiographic determinations of left ventricular volume is related to the distortion in left ventricular cross-sectional anatomy induced by right ventricular volume overload.[17] Thus, observations made in our laboratory and by others[17] have demonstrated that, in patients with an atrial septal defect, the left ventricle converts from a circular configuration in the short axis plane at end-diastole to a shape in which the interventricular septum is flattened or bowed into the left ventricular cavity. Accordingly, echocardiographic measurements of left ventricular size that utilize recordings that traverse the center of the flattened or indented interventricular septum would invariably reveal a diminished left ventricular diameter, whereas left ventricular volume obtained with single plane right anterior oblique left ventricular cineangiography would be relatively uninfluenced by such geometric changes. If the left ventricle were indeed underfilled, one would anticipate a symmetric reduction in its size rather than a decrease limited to one plane. Therefore, our data provide no evidence of a generalized reduction in left ventricular size due to underfilling of this cardiac chamber but indicate that the decreased left end-diastolic dimension recorded on echocardiography is a reflection of flattening or bowing of the interventricular septum caused by right ventricular enlargement.

Alleged diminution of left ventricular stroke volume: Just as it was assumed that the shunting of blood from the left to the right atrium through an atrial septal defect would result in a marked reduction in left ventricular size, it was believed that a diminished stroke volume would invariably occur in this disorder. However, previously reported measurements of systemic cardiac output in patients with an atrial septal defect have varied from normal,[15,18] to low normal[19,20] or diminished.[21] Measurements reported in many of these studies were based on determination of cardiac output by the Fick method, which tends to underestimate systemic flow and overestimate pulmonary flow as a result of the narrowed arteriovenous oxygen differences between the pulmonary vein and the pulmonary artery associated with large left to right shunts.[3] Further, the study with abnormally low cardiac output values[21] was limited to adult patients with an atrial septal defect. In our study, stroke volume and cardiac output were similar in patients with an atrial septal defect and in normal subjects as assessed with both the indicator-dilution technique as well as cineangiographic methods, as was echographic shortening fraction. Because interventricular septal motion in the echogram was paradoxic in all patients with an atrial septal defect due to right ventricular volume overload, the normal shortening fraction must represent posterior wall hyperkinesia. That overall left ventricular function is not altered in patients with an atrial septal defect is supported by the failure of previous investigations to demonstrate any consistent abnormality of performance[20–23] unless coexistent mitral valve disease or systemic hypertension was present. Thus, our study revealed no evidence of left ventricular dysfunction in the setting of chronic atrial septal defect.

Acknowledgment

We acknowledge the expert technical assistance of Alexander Neumann and Lynn Weinert and the secretarial support of Betty Paro.

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Significance of Left Axis Deviation in Patients with Chronic Left Bundle Branch Block

RAMESH C. DHINGRA, MD, FACC
FERNANDO AMAT-Y-LEON, MD, FACC
CHRISTOPHER WYNDHAM, MD
SIVRAM S. SRIDHAR, MD
DELON WU, MD, FACC
PABLO DENES, MD, FACC
KENNETH M. ROSEN, MD, FACC

Chicago, Illinois

Forty-nine patients with chronic left bundle branch block and a normal frontal axis were compared with 53 patients with left bundle branch block and left axis deviation. The following clinical variables were more frequent ($P < 0.05$) in patients with left axis deviation: greater age, exertional angina, congestive heart failure, cardiomegaly, cardiac functional class II to IV, coronary artery disease and presence of organic heart disease. Absence of organic heart disease (primary conduction disease) was seen only in patients with a normal axis. Patients with left axis deviation had longer ($P < 0.05$) mean P-R, A-H and H-V intervals and atrial and atrioventricular (A-V) nodal effective refractory periods. All patients were prospectively followed up for 30 to 2,271 days with a mean ± standard error of the mean follow-up period of 538 ± 72 for the group with a normal axis and 604 ± 72 days for the group with left axis deviation (difference not significant). A-V block developed in three patients (6 percent) with left axis deviation and in none of those with a normal axis. The cumulative 4 year mortality rate for the entire group approached 75 percent. The patients with left axis deviation had greater cardiovascular mortality ($P < 0.05$).

In conclusion, among patients with left bundle branch block, those with left axis deviation have a greater incidence of myocardial dysfunction, more advanced conduction disease and greater cardiovascular mortality than those with a normal axis.

The clinical significance of left axis deviation in patients with chronic left bundle branch block has been controversial. Some studies[1–3] have suggested that patients with left bundle branch block and left axis deviation have a greater incidence of myocardial dysfunction or more widespread conduction disease, or both, than those with a normal frontal axis. Others[4–6] have reported no significant clinical or electrophysiologic differences in these two groups of patients with left bundle branch block.

In an attempt to resolve this controversy regarding the significance of left axis deviation in patients with left bundle branch block, we report our total experience with left bundle branch block, comparing patients with a normal axis and those with left axis deviation in regard to clinical, electrocardiographic and electrophysiologic abnormalities. In addition, we report prospective observations concerning the life history of these patients.

Methods

Definitions: The criteria for the electrocardiographic diagnosis of left bundle branch block[7] included a QRS duration of 0.12 second or greater, a predominantly negative QRS deflection in lead V_1 and a notched widened R wave in lead V_6. Left axis deviation was considered present when the mean frontal QRS axis was between −30° and −90°. The mean frontal axis was considered normal if the axis was between −29° and +90°.[7]

From the Cardiology Section, Department of Medicine, Abraham Lincoln School of Medicine, University of Illinois College of Medicine and West Side Veterans Administration Hospital, Chicago, Illinois. This study was supported in part by Training Grant HL-05789-08 and Grant HL-18794-02, from the National Institutes of Health, Bethesda, Maryland, and Basic Institutional Support, MRIS 1828, West Side Veterans Administration Hospital, Chicago, Illinois. Manuscript received February 27, 1978; revised manuscript received May 2, 1978, accepted May 3, 1978.

Address for reprints: Ramesh C. Dhingra, MD, University of Illinois Hospital, Cardiology Section, PO Box 6998, Chicago, Illinois 60680.

TABLE I

Clinical Data in 102 Patients With Left Bundle Branch Block

	Normal Axis		Left Axis		
	no.	%	no.	%	*P* Value
Patients (no.)	49	48	53	52	
Sex					
Male	37	76	40	75	NS
Female	12	24	13	25	NS
Clinical finding					
Angina	13	26	24	45	<0.05
CHF	21	42	36	68	<0.01
Cardiomegaly	31	63	44	85	<0.05
NYHA class I	24	49	8	15	<0.001
NYHA class II to IV	25	51	45	85	<0.001

CHF = congestive heart failure; NS = not significant; NYHA = New York Heart Association; *P* = probability.

TABLE II

Clinical Diagnosis in 102 Patients With Left Bundle Branch Block

Heart Disease	Normal Axis (no. = 49)		Left Axis (no. = 53)		
	no.	%	no.	%	*P* Value
Primary conduction disease	8	16	0	0	<0.05
Arteriosclerotic	15	31	28	53	<0.05
Hypertensive	17	35	10	19	NS
Valvular	3	6	7	13	NS
Primary myocardial disease	6	12	7	13	NS
Other	0	0	1	2	NS

NS = not significant; *P* = probability.

Patient selection: The study group consisted of 102 patients with chronic left bundle branch block. Patients with prior second or third degree atrioventricular (A-V) block and those with acute myocardial infarction were excluded. There were 77 men and 25 women. These patients were studied as part of our prospective study of chronic intraventricular conduction defects at the Chicago Westside Medical Center (Cook County Hospital, the West Side Veterans Administration Hospital and the University of Illinois Hospital). The 102 patients with left bundle branch block were detected, studied and followed up between January 1970 and August 1977. The study group consisted of consecutively studied patients who volunteered for the study. Patients with left bundle branch block and severe debilitating disease were not considered candidates for electrophysiologic study and prospective follow-up.

The initial evaluation of patients included a history, physical examination, chest X-ray film and serial electrocardiograms. A clinical diagnosis was established for each patient on the basis of this evaluation. Previously described criteria were utilized for the diagnosis of organic heart disease.[8] Arteriosclerotic heart disease was diagnosed if the patient had a history of typical exertional angina, a previous diagnosis of definite myocardial infarction or a positive coronary arteriogram. Hypertensive heart disease was diagnosed if two or more blood pressure recordings indicated a systolic pressure greater than 140 mm Hg and diastolic pressure greater than 100 mm Hg. If a patient had both arteriosclerotic and hypertensive cardiovascular disease, the most clinically significant diagnosis was listed. "Primary conduction disease" was diagnosed if heart size was normal and there was no clinical evidence of organic heart disease, with the exception of an intraventricular conduction defect.

Electrophysiologic study: Informed written consent was obtained before electrophysiologic study. His bundle electrograms utilizing previously described catheter techniques were recorded in all patients.[9] Cardiac drugs (digoxin, antiarrhythmic agents and propranolol, if feasible) were withheld for at least 48 to 72 hours before the study. Measurements of A-H (A-V nodal conduction) and H-V (His-Purkinje conduction) intervals were made at paper speeds of 200 mm/sec and reflect the mean of 10 consecutive sinus beats. Normal values[9] (mean ± 2 standard deviations) utilized for these intervals were as follows: A-H, 92 ± 38 msec; H-V, 43 ± 12 msec. Sinus nodal recovery time (normal 988 ± 692 msec)[9] was measured as the mean of three determinations after sudden cessation of atrial pacing at a rate of 130/min. Refractory periods of the atrium and A-V node were measured with the atrial extrastimulus technique during sinus rhythm, as previously described by Denes et al.[10] Mean sinus cycle lengths were similar in the two groups (see later). His bundle pacing was not routinely performed.

Patient follow-up: Follow-up studies were similar to those previously described by our laboratory.[11–17] After initial study, all patients were prospectively followed up in conduction disease clinics at intervals of 1 to 3 months. A complete history and physical examination, together with a 12 lead electrocardiogram, were obtained at each clinic visit. Patients were hospitalized on development of symptoms, and prolonged portable electrocardiographic monitoring was utilized for detection of suspected transient bradyarrhythmias. In patients with developing A-V block, an attempt was made to define the site of block utilizing clinical and surface electrocardiographic data. His bundle electrograms were repeated in one of the three patients manifesting A-V block. Permanent pacemakers were implanted only in symptomatic patients with documented bradyarrhythmias or in those with recurrent syncope due to unknown causes. No patient was lost to follow-up.

Statistical analysis: All information at the time of initial evaluation and subsequent clinic visits was keypunched and stored in retrievable database discs. Specifically designed programs were used for data recall and statistical analysis. A standard *t* test was used to test the significance of differences in means and a two-by-two chi square method for frequency data analysis. Data on survival rates were analyzed utilizing previously described life table methods.[18]

Results

Clinical data (Table I): There were 49 patients with a normal QRS axis (−20° to +90°) (mean ± standard deviation +23° ± 35°) and 53 with left axis deviation (−30° to −90°) (mean −51° ± 18°). There were 37 men and 12 women with a normal axis and 40 men and 13 women with left axis deviation (difference not significant). The mean age (± standard error of the mean) was 58 ± 1.7 years (range 36 to 83) for the group with a normal axis and 66 ± 1.5 years (range 41 to 87) for the group with left axis deviation ($P < 0.001$).

The frequency of selected clinical findings is presented in Table I. Exertional angina, clinically diagnosed congestive heart failure and cardiomegaly on chest X-ray examination were significantly more com-

TABLE III

Electrocardiographic Findings in 102 Patients With Left Bundle Branch Block

	Normal Axis (no. = 49)				Left Axis Deviation (no. = 53)				
	Range	Mean ± SEM	no.	%	Range	Mean ± SEM	no.	%	*P* Value
P-R interval (sec)	0.14–0.28	0.19 ± 0.005	...	...	0.14–0.42	0.23 ± 0.007	...	...	<0.001
QRS duration (sec)	0.12–0.18	0.145 ± 0.002	...	...	0.12–0.20	0.141 ± 0.002	...	...	NS
Q wave in lead I, aVL or V_6	...	...	8	16	...	...	13	24	NS
S wave in lead V_6	...	...	17	35	...	...	26	49	NS
PVC (>3/min)	...	...	6	15	...	...	15	29	NS

NS = not significant; *P* = probability; PVC = premature ventricular complex; SEM = standard error of the mean.

mon in the group with left axis deviation than in the group with a normal axis. More patients in the latter than in the former group were in New York Heart Association cardiac functional class I, whereas the majority of patients with left axis deviation had cardiac symptoms (classes II to IV) (P <0.001).

Etiology of left bundle branch block: The clinical diagnoses in the 102 patients with left bundle branch block are listed in Table II. Primary conduction disease (absence of apparent organic heart disease) was significantly more common in the patients with a normal axis, occurring in eight patients in this group. No patient with left bundle branch block and left axis deviation had a clinical diagnosis of primary conduction disease (P <0.05). Arteriosclerotic heart disease was significantly more common in the group with left axis deviation, occurring in 28 of 53 patients (53 percent), whereas it occurred in only 15 of 49 patients (31 percent) with a normal axis (P <0.05). The prevalence of hypertensive cardiovascular disease, valvular heart disease and primary myocardial disease was not significantly different in the two groups.

Electrocardiographic data (Table III): The mean P-R interval was 0.19 ± 0.005 second (range 0.14 to 0.28) for the group with a normal axis, and 0.23 ± 0.007 second (range 0.14 to 0.42) for the group with left axis deviation (P <0.001). There was no significant difference in regard to QRS duration and the presence or absence of atypical left bundle branch block (Q wave in leads I, aVL and V_6 or S wave in lead V_6). Premature ventricular complexes, detected in the resting 12 lead electrocardiogram, were more common in the group with left axis deviation, but the difference was not statistically significant.

Electrophysiologic data (Table IV): There was no significant difference in heart rate at the time of electrophysiologic study between the patients with a normal axis and those with left axis deviation. The mean A-H interval was 104 ± 4.8 msec (range 58 to 195) for the group with normal axis and 130 ± 7.7 msec (range 55 to 320) for the group with left axis deviation (P <0.01). However, the incidence of A-H prolongation was not significantly different in the two groups. The mean H-V interval was 60 ± 1.5 msec (range 39 to 93) for the group with a normal axis and 67 ± 2.4 msec (range 35 to 125) for the group with left axis deviation (P <0.01). The incidence of H-V prolongation was greater in patients with left axis deviation (P <0.02). Both the atrial effective refractory period and the A-V nodal effective refractory period were longer in the patients with left axis deviation (P <0.01 and P <0.05, respectively). Significant changes in axis were not observed in either group during extrastimulus testing. There was no significant difference in sinus nodal recovery time between the two groups.

A-V block and pacemakers: The overall follow-up period ranged from 30 to 2,271 days (mean ± standard error of the mean 538 ± 72 days for the group with a normal axis and 604 ± 72 days for the group with left axis deviation [difference not significant]). Three patients (3 percent) manifested second or third degree A-V block during the follow-up period; all three had left axis

TABLE IV

Electrophysiologic Data in 102 Patients With Left Bundle Branch Block

	Normal Axis (no. = 49)				Left Axis Deviation (no. = 53)				
	Range	Mean ± SEM	no.	%	Range	Mean ± SEM	no.	%	*P* Value
Heart rate (beats/min)	45–108	76 ± 2.1	49	...	50–130	81 ± 2.1	53	...	NS
A-H interval (msec)	58–195	104.3 ± 4.8	48	...	55–320	130.2 ± 7.7	52	...	<0.01
A-H interval (>130 msec)			10	21			15	28	NS
H-V interval (msec)	39–93	60.1 ± 1.5	49	...	35–125	67.3 ± 2.4	53	...	<0.01
H-V interval (>55 mesc)			27	55			41	77	<0.02
Atrial ERP (msec)	150–320	237.3 ± 7.1	35	...	150–420	272.4 ± 10.6	35	...	<0.01
A-V nodal ERP (msec)	230–490	343.2 ± 13.5	23	...	270–500	400.4 ± 23.4	22	...	<0.05
Sinus recovery time (msec)	555–1600	964.0 ± 31.1	38	...	590–2200	1047.0 ± 47.1	40	...	NS

ERP = effective refractory period; NS = not significant; *P* = probability; SEM = standard error of the mean.

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TABLE V

Comparative Cumulative Mortality Rate in 102 Patients With Left Bundle Branch Block

	Normal Axis (no. = 49)		Left Axis Deviation (no. = 53)		
	Mortality Rate ± SEM (%)	Patients Exposed to Risk of Dying	Mortality Rate ± SEM (%)	Patients Exposed to Risk of Dying	*P* Value
Cumulative mortality					
1st year	29 ± 7.4	38	27 ± 6.4	48	NS
2nd year	41 ± 8.7	18	47 ± 7.4	27	NS
3rd year	41 ± 8.7	10	62 ± 8.5	14	<0.05
4th year	65 ± 11.7	8	74 ± 9.1	7	NS
Mortality due to sudden death					
1st year	20 ± 6.6	36	19 ± 6.4	37	NS
2nd year	29 ± 8.5	18	28 ± 8.1	19	NS
3rd year	29 ± 8.5	10	28 ± 8.1	11	NS
4th year	57 ± 13.7	8	61 ± 14.8	7	NS
Cardiovascular mortality					
1st year	22 ± 7.1	37	25 ± 6.3	48	NS
2nd year	34 ± 8.5	18	42 ± 7.7	27	NS
3rd year	34 ± 8.5	10	57 ± 8.6	16	<0.05
4th year	60 ± 12.9	8	68 ± 9.2	8	NS

NS = not significant; *P* = probability; SEM = standard error of the mean.

deviation. The block was spontaneous in two and was related to digitalis intoxication in one. The site of block was distal to the His bundle in both patients with spontaneous block, occurring on days 406 and 1,034 of the follow-up period, respectively. Digitalis-induced advanced A-V block proximal to the His bundle occurred in the third patient on day 925 of the follow-up period. All three patients manifesting A-V block had arteriosclerotic heart disease. No patient with a normal axis had A-V block.

Insertion of a permanent pacemaker was required in 10 patients (10 percent), 5 from each group (difference not significant). In the normal group, the pacemaker was implanted because of symptomatic sinoatrial dysfunction (two patients), recurrent syncope of unknown cause (two patients) and the post cardiac surgery status (one patient). In the group with left axis deviation, the pacemaker was implanted because of A-V block distal to the His bundle (two patients), recurrent syncope of unknown cause (one patient), digitalis-induced sinus bradycardia (one patient) and status after aortic valve replacement (one patient).

Mortality: Forty-five of the 102 patients (44 percent) died, 18 (36 percent) from the group with a normal axis (12 suddenly) and 27 (51 percent) from the group with left axis deviation (11 suddenly) (difference not significant). The cardiovascular mortality (including sudden death) was significantly greater in patients with left axis deviation, occurring in 25 (47 percent) of this group compared with 13 (26 percent) of those with a normal axis ($P < 0.05$).

Annual cumulative total mortality rates (through 4 years), mortality due to sudden death as well as total cardiovascular mortality (including sudden death) utilizing actuarial methods are presented in Table V. There was no significant difference in cumulative mortality rates for the first 2 years when comparing the two groups. Both the cumulative mortality and cardiovasuclar mortality rates were significantly higher in patients with left axis deviation during the third year of follow-up.

Discussion

Left axis deviation and severity of heart disease and conduction disease: It has been suggested that among patients with left bundle branch block those with left axis deviation have more advanced heart disease and conduction system disease than those with a normal axis. Beach et al.[2] reported on 10 patients with left bundle branch block and a normal axis who had normal hemodynamic and angiographic findings. They also reported on 17 other patients with left bundle branch block and definite clinical heart disease, 10 of these having left axis deviation and 7 a normal axis (no hemodynamic studies were performed in this group). They suggested that in patients with left bundle branch block left axis deviation reflected the presence of significant underlying organic heart disease and a poorer prognosis than that of patients with a normal axis. In contrast is the report of Haft et al.[4] on results of hemodynamic and angiographic studies in 14 patients with left bundle branch block with a normal axis and 10 with left axis deviation. The severity of myocardial dysfunction and prevalence of coronary artery disease was similar in both groups of patients, suggesting that the left axis deviation in these patients did not have malignant implications.

The results of our study confirm the observation of Beach et al.[2] In our series, left axis deviation in patients with left bundle branch block was associated with a significantly greater prevalence of myocardial dysfunction, as suggested by cardiomegaly, congestive heart failure and functional classes II to IV. All of our patients with primary conduction disease (bundle branch block without demonstrable organic heart disease) had a normal axis, as in the study of Beach et al.[2] Whether this will prove true of all such patients is not known. The finding of left axis deviation in a patient with left bundle

branch block suggests that organic heart disease will be found, if looked for; arteriosclerotic heart disease was significantly more common in such patients.

Left axis deviation and H-V interval (trifascicular disease): It has been suggested that patients with left axis deviation and left bundle branch block have bilateral bundle branch (trifascicular) disease, as indicated by H-V prolongation. Spurrell et al.[3] reported the results of His bundle studies in nine patients with left bundle branch block, four with a normal axis and five with left axis deviation. The H-V interval was prolonged (ranging from 70 to 95 msec) in all five patients with left axis deviation, suggesting conduction delay in the right bundle branch (trifascicular disease). In contrast, the H-V interval was within normal limits in all four patients with a normal axis. Spurrell et al. implied that the presence of left axis deviation with left bundle branch block reflected widespread conduction disease and might be an indication for permanent pacemaker insertion in symptomatic patients. On the other hand, Rosen et al.[5] reported on three groups of patients with left bundle branch block—those with a normal, intermediate or prolonged H-V interval. The mean frontal QRS axis was not significantly different in the three groups. However, Rosen et al. did not compare mean H-V intervals in the patients with a normal axis and left axis deviation in their early series.

Our current study is in partial agreement with the results of Spurrell et al.[3] Both the mean H-V interval and incidence of H-V prolongation were significantly greater in patients with left bundle branch block and left axis deviation. Forty-one of our 53 patients (77 percent) with left axis deviation had a prolonged H-V interval. However, 27 of our 49 patients (55 percent) with a normal axis also had H-V prolongation. The H-V prolongation seen in both groups could be related to His bundle disease distal to the recording site, right bundle branch disease or right ventricular stretch (with a blocked left bundle branch).

The mean A-H interval was significantly longer in the group with left axis deviation, partly contributing to the longer P-R intervals found in this group, and suggesting a greater prevalence of A-V nodal disease in these patients. The patients with left axis deviation also had significantly longer atrial refractory periods, suggesting a greater prevalence of atrial disease in these patients. In summary, we found more evidence of widespread conduction disease in the atrium, A-V node and His-Purkinje system in patients with left bundle branch block and left axis deviation than in those with a normal axis, probably reflecting the greater amount of organic heart disease in this group.

Prognostic significance of left axis deviation in patients with left bundle branch block: Information regarding this is limited. Wiberg et al.[6] reported retrospective follow-up results in 163 patients with left bundle branch block—90 with a normal axis and 32 with left axis deviation. Twenty-five patients (27 percent) with a normal axis and 10 (31 percent) with left axis deviation died over a follow-up period of 18 to 42 months. The yearly mortality rate (nonactuarial) was 20 percent for the normal group and 32 percent for the group with left axis deviation. Cardiovascular mortality and the incidence of sudden death were not specified in their study. In our series, the cumulative mortality rate was high for both patient groups, approaching 75 percent at 4 years. Although the frequency of sudden death was similar in the two groups, total cardiovascular mortality was significantly more common in patients with left axis deviation.

Progression to complete A-V block: There is little information concerning the progression of left bundle branch block to advanced or complete heart block. Rotman et al.[19] reported only one occurrence of heart block in 125 asymptomatic Air Force personnel with left bundle branch block over a mean follow-up period of 8.8 ± 4.8 years. In the series of Wiberg et al.[6] complete heart block occurred in 3 of 138 patients (2.3 percent) with left bundle branch block over an unspecified follow-up period. Neither of these reports specified either the prior frontal QRS axis in the patients manifesting complete heart block or the site of A-V block. Spontaneous A-V block occurred in only two patients of our series, an incidence similar to that of Wiberg et al. The site of block in both of our patients was trifascicular (distal to the His bundle). Patients manifesting A-V block in our study had arteriosclerotic heart disease. One may speculate that some of the sudden deaths in our patients may have been secondary to the sudden development of trifascicular block. Our recently reported data[17] suggest that the most common cause of sudden death in patients with chronic bifascicular block is ventricular dysrhythmia rather than trifascicular block.

Mechanism for left axis deviation in left bundle branch block: This study sheds little light on the mechanism or mechanisms responsible for left axis deviation in patients with left bundle branch block. With complete left bundle branch block, the impulse enters the ventricles by way of the right bundle branch.[20–22] The right ventricle is activated in its usual fashion. The impulse crosses the ventricular septum at one or more sites and then appears to enter the left ventricular distal Purkinje system and is distributed to the left ventricle.[22] The mean frontal QRS axis in left bundle branch block presumably reflects the site or sites of impulse crossing in the septum and the distribution of the impulse within the left ventricle. Left axis deviation in a patient with left bundle branch block presumably reflects abnormalities in activation of the left ventricle, which could reflect a septal, distal Purkinje system or a parietal left ventricular abnormality. The thinner anterior fascicle could be more prone to injury because of ventricular stretch, which might be more severe in the group with left axis deviation. Our study suggests that ventricular disease may interfere in some way with distribution of the impulse within the left ventricle, with resulting left axis deviation. However, it is clear that left ventricular disease may occur in a patient with left bundle branch block in association with either a normal QRS axis or left axis deviation.

Clinical implications: The following conclusions are suggested by our study. In patients with left bundle

branch block left axis deviation is associated with a greater incidence of myocardial dysfunction and more evidence of conduction disease than is a normal axis. Although progression of conduction disease was uncommon in our patients with left bundle branch block, it was noted only in patients with left axis deviation, suggesting that this group is at somewhat greater risk for the development of A-V block. A normal axis in patients with left bundle branch block, although usually associated with organic disease, may be associated with no additional evidence of organic heart disease. The mechanism of left axis deviation in patients with left bundle branch block remains speculative.

Acknowledgment

We appreciate the secretarial assistance of Julia V. Cancel and Laurie Nelson in the preparation of this manuscript.

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Cardiac Biopsy Evidence for a Cardiomyopathy Associated With Symptomatic Mitral Valve Prolapse

JAY W. MASON, MD
FRANCIS H. KOCH, MD
MARGARET E. BILLINGHAM, MD
ROGER A. WINKLE, MD, FACC

Stanford, California

Right ventricular endomyocardial biopsy was performed in 14 patients with mitral valve prolapse to determine the existence of an associated cardiomyopathic process. All 14 patients had echocardiographic, angiographic or auscultatory evidence of mitral valve prolapse, and all were symptomatic. The group had a high incidence rate of conduction system abnormalities (50 percent) and arrhythmias (64 percent), but only one patient had a significant hemodynamic abnormality. Light microscopy revealed an increase in endocardial and interstitial fibrosis in eight patients (57 percent). Electron microscopy, performed in 11 patients, showed mitochondrial degenerative changes in all 11. Nuclear chromatin clumping, intracell edema and myocyte degeneration were frequently present. It is concluded that endomyocardial and myocardial abnormalities exist in some symptomatic patients with idiopathic mitral valve prolapse.

The nature of the disease process responsible for the clinical syndrome of mitral valve prolapse is not clear. In some patients one can distinguish an associated cardiac disorder, such as papillary muscle dysfunction due to ischemia,[1] obstructive or nonobstructive hypertrophic cardiomyopathy,[2] atrial septal defect[3] or rheumatic valve disease.[4,5] However, in most patients with mitral valve prolapse, myxomatous degeneration of the valve leaflets is probably responsible for the valve dysfunction,[6] and these patients are said to have *primary* mitral valve prolapse.

Many patients with primary mitral valve prolapse have atypical chest pain,[7] arrhythmias,[8] conduction abnormalities,[9] angiographically abnormal left ventricular contraction patterns[10–14] and ischemic electrocardiographic changes on treadmill testing,[15] as well as abnormal electrocardiographic, metabolic and hemodynamic responses to atrial pacing.[16] Most of these symptoms and findings cannot be satisfactorily explained on the basis of the valve lesion alone. This complex of findings in primary mitral valve prolapse has led some investigators to suspect that a myocardial disorder is an important component of the syndrome in some patients. In this investigation we utilized the technique of right ventricular endomyocardial biopsy[17,18] to evaluate the possibility of a cardiomyopathic process in a group of patients with mitral valve prolapse.

Methods

Patients: Fourteen patients with primary mitral valve prolapse underwent right ventricular endomyocardial biopsy. All patients gave informed consent for the endomyocardial biopsy procedure in accordance with the Stanford University Medical Committee on the Use of Human Subjects in Research. All of the patients were referred because of symptoms (chest pain, palpitation, syncope, dyspnea or fatigue) thought to be related to the syndrome of mitral valve prolapse (Table I).

All patients had a nonejection systolic click or an apical systolic murmur, or both (Table I). Five patients (Cases 1 to 3, 5 and 6) had prolapse of the mitral

From the Division of Cardiology, and the Department of Pathology, Stanford University School of Medicine, Stanford, California. This work was supported in part by Grant HL-5866 from the National Institutes of Health, Bethesda, Maryland. Manuscript received February 13, 1978; revised manuscript received May 24, 1978, accepted May 24, 1978.

Address for reprints: Jay W. Mason, MD, Cardiology Division, Stanford University School of Medicine, Stanford, California 94305.

TABLE I

Patients With Mitral Valve Prolapse: Echocardiographic, Angiographic, Hemodynamic and Electrocardiographc Findings

Case no.	Age (yr) & Sex	Non-ejection Click*	Murmur†	Prolapse on Echo	Prolapse on Angio	LV Cath/ Angio Abnormality	Coronary Angio Abnormality‡	Electrocardiographic Abnormalities: ST-T	Conduction	Arrhythmias	Ischemia on Treadmill§
1	56M	−	+	+	+	LVE, LVEDP	ND	+(T)	−	A Fl, A fib	ND
2	37F	+	−	+	+	LVE, LV seg	−	+(T)	LAD	VT	−
3	26F	+	+	+	+	−	−	+(T)	↑Q-T	SB, SVT	−
4	50F	+	+	−	+	−	ND	−	↑P-R, RBBB	VPC, A Fl	ND
5	60F	+	+	+	+	LVE, LV seg	−	+(ST-T)	−	VPC, APC, SVT	−
6	48F	+	+	+	+	−	ND	+(ST-T)	RBBB	−	+
7	61F	+	−	ND	+	−	−	−	↑Q-T	−	ND
8	19F	+	−	+	ND	ND	ND	−	−	SB, SVT	−
9	45F	+	+	+	ND	ND	ND	+(ST-T)	−	APC, VPC	+
10	46M	+	+	−	+	−	−	−	−	−	−
11	40F	+	+	ND	−	−	−	−	−	SB	ND
12	49F	+	+	ND	−	−	−	−	RBBB	−	−
13	47F	+	+	+	−	−	−	−	−	−	ND
14	60F	+	+	−	−	−	ND	−	↑Q-T	SVT, VB, SB, A f	ND

* Systolic click occurring at least 0.04 second after onset of the first heart sound.
† Systolic apical murmur, either late or pansystolic.
‡ Abnormality defined as greater than 50 percent luminal arterial narrowing.
§ Standard Bruce protocol used. Ischemic abnormality defined as 1 mm or more horizontal or downsloping S-T segment depression below a line drawn from the onset of the P wave to the onset of the QRS complex.
+ abnormality present; − abnormality absent.
A fib = atrial fibrillation; A Fl = atrial flutter; Angio = angiography; APC = frequent premature atrial complexes; Cath = catheterization; Echo = echocardiography; LAD = left axis deviation; LV = left ventricular; LVE = left ventricular enlargement; LVEDP = left ventricular end-diastolic pressure abnormality; LV seg = left ventricular segmental contraction abnormality; ND = study not done; P-R = first degree atrioventricular block; Q-T = prolonged Q-T interval; RBBB = pattern of right bundle branch block; SB = sinus bradycardia; ST-T = nonspecific ST-T changes; SVT = supraventricular tachycardia; T = abnormal T wave inversion; VB = ventricular bigeminy; VPC = frequent ventricular premature complexes; VT = ventricular tachycardia.

valve identified in both the echocardiogram and left ventriculogram. Three patients (Cases 8, 9 and 13) had a positive echocardiogram without left ventriculographic evidence of prolapse, and two patients (Cases 4 and 10) had a positive ventriculogram only. Three patients (Cases 11, 12 and 14) had no echocardiographic or ventriculographic evidence of prolapse. All three had a normal left ventriculogram in a single right anterior oblique projection, and two (Cases 11 and 12) did not undergo echocardiography. However, all three had a mid systolic click and late apical systolic murmur typical of mitral valve prolapse.

Tricuspid valve prolapse occurs in patients with mitral valve prolapse.[19] It is thus conceivable that our patients could have had tricuspid regurgitation that resulted in right ventricular pathologic changes. However, no patient had physical or echocardiographic findings suggesting tricuspid regurgitation, and no patient studied hemodynamically had abnormal right atrial pressure.

Echocardiography and ventriculography: Echocardiographic mitral valve prolapse was diagnosed only when the proper transducer position was used[20] and when the systolic mitral valve echo bowed posteriorly at least 2 mm from a line drawn between the C (closing) and D (opening) points of the mitral valve tracing.[20,21] All left ventriculograms were obtained in a single 30° right anterior oblique projection. Angiographic mitral valve prolapse was diagnosed according to the criteria of Ranganathan et al.[22]

Echocardiograms and left ventriculograms were retrospectively reviewed for the presence of mitral valve prolapse by two of us and two independent observers. Prolapse was judged present only if all four observers agreed. On the basis of echocardiogram, chest radiograph and hemodynamic study, only Patient 1 (Table I) had significant hemodynamic derangement.

Right ventricular endomyocardial biopsy: This was performed using a previously described percutaneous catheter technique developed at this institution.[18] The bioptome, 50 cm long with a 9F diameter, has a pair of cutting jaws at the distal end; it is advanced by way of the right internal jugular vein, across the tricuspid valve to the right ventricle, from which specimens are serially obtained. The technique is associated with a remarkably low morbidity.[17,18] In each patient three or four myocardial samples 2 to 4 mm in diameter were removed from the apical portion of the right ventricular septum. Depending on the size of each sample, one or two biopsy specimens were immediately placed in 10 percent buffered formalin, and one or two in 2.5 percent buffered glutaraldehyde, after prompt removal from the biopsy forceps. Light microscopy was performed on the formalin-preserved specimens using hematoxylin-eosin and Masson's trichrome stains. The glutaraldehyde-preserved specimens were postfixed with cold 1 percent osmium tetroxide, stained with 2 percent uranyl acetate and embedded in epoxy resin to be sectioned for electron microscopy. Light and electron microscopic observations were made by three of us, and the recorded interpretations represent unanimous agreement of the three observers.

Control specimens: The specimens from the patients with mitral valve prolapse were examined together with control samples obtained at transplantation from the normal hearts of 10 cardiac donors. These samples were obtained from the right ventricular septum after the donor hearts had been excised from the donor, cooled in iced saline solution and partially sutured into the recipient. After removal, these samples were handled in the same manner as the specimens obtained from the patients with prolapse. The mean age of the donor group was 24.8 years (range 15 to 44 years). Specimens from the 10 oldest donors with complete pathologic data available

TABLE II

Pathologic Findings

Case no.	Light Microscopy		Electron Microscopy			
	Fibrosis	Myocyte Abnormality	Myocyte Degeneration	Mitochondrial Degeneration	Nuclear Chromatin Clumping	Edema
			Patients With Mitral Valve Prolapse			
1	−	−	++	+++	+	+
2	−	−	ND	ND	ND	ND
3	++	−	ND	ND	ND	ND
4	−	+++	−	++	+	−
5	−	−	−	+++	±	±
6	−	−	−	+++	++	−
7	+	+	++	+++	−	+++
8	+	+	+++	+++	++	−
9	−*	−*	+	++	++	−
10	+	++	−	+++	±	−
11	+++	−	−	+	−	++
12	++	+	−	++	±	−
13	++	−	−	++	−	−
14	+	−	ND	ND	ND	ND
			Control Subjects			
1	−	−	−	±	±	−
2	−	−	−	+	−	−
3	−	+	−	+++	+	−
4	+	−	−	+	+	−
5	−	−	−	−	−	−
6	−	−	−	±	−	−
7	∓	−	−	±	−	±
8	−	−	−	+	−	−
9	−	−	+	++	−	±
10	−	−	−	+	±	−

* Small sample.
− = absent; ± = questionably present; + = mild abnormality present; ++ = marked abnormality present; +++ = severe abnormality present.
ND = study not done.

were selected for this study to minimize age-related differences. All 24 specimens (from patient and control hearts) were examined together, in blinded manner, so that the observers were unaware of the identity of the patient from whom the samples were obtained.

Results

Clinical features: The study group of 14 patients with mitral valve prolapse included 12 women and 2 men aged 19 to 61 years (mean 46 years) (Table I). Eighty percent (11 of 14) of the patients had atypical chest pain, and more than half (8 of 14) had both palpitation and syncope or presyncope. One third (4 of 14) of the patients complained of symptoms suggestive of left ventricular failure (dyspnea and fatigue), although only one of these four patients had roentgenographic or catheterization evidence of left heart failure. That patient (Case 1) had severe mitral regurgitation due to surgically documented mitral chordal rupture associated with myxomatous degeneration of the mitral valve. Two other patients (Cases 2 and 5) had mild left ventricular enlargement and segmental contraction abnormalities without a hemodynamic abnormality.

There was a large incidence of electrocardiographic abnormalities in these patients (Table I). S-T segment and T wave abnormalities and both ventricular and supraventricular arrhythmias, including tachyarrhythmias, were common. Two of the nine patients who underwent treadmill exercise testing had ischemic S-T segment changes. None of the eight who underwent coronary arteriography had significant coronary arterial narrowing. Neither stress testing nor coronary arteriography was performed in four patients, all women aged 50 years or less, who had atypical chest pain. In these patients the pain was so atypical or trivial that the procedures were not considered indicated or relevant.

Pathologic findings: The biopsy specimens were examined for abnormalities under light and electron microscopy. Table II summarizes the pathologic findings in the patients with mitral valve prolapse and the control subjects. Abnormal endocardial and interstitial fibrosis, at times severe, was seen on light microscopy of the specimens in 8 (57 percent) of the 14 patients with mitral valve prolapse (Fig. 1). When fibrosis was present, it was seen in both the endocardium and the interstitium and was detected with both light and electron microscopy. Light microscopy was used to judge the severity of fibrosis. Mild increases in endocardial fibrosis were thought to be present in two (20 percent) of the control hearts. Focal myocyte hypertrophy was observed under light microscopy in specimens from 5 (36 percent) of 14 patients with mitral valve prolapse and was questionably present in only one control specimen.

The biopsy specimens of 11 patients with prolapse and all 10 control subjects were evaluated with electron

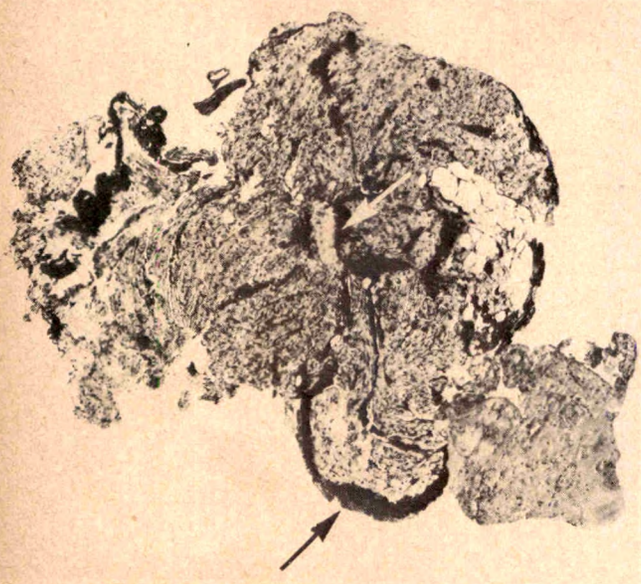


FIGURE 1. Patient 11. This endomyocardial biopsy specimen shows a marked increase in endocardial **(dark arrow)** and interstitial **(white arrow)** fibrosis. (Masson's trichrome stain ×48, reduced by 18 percent.)

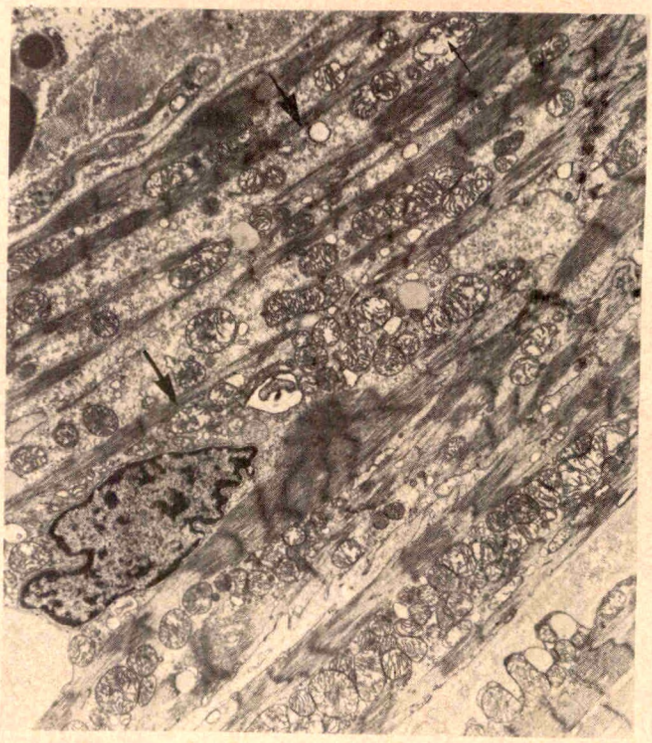


FIGURE 2. Patient 8. Electron micrograph showing an area of advanced myocyte dystrophy, with myofibrillar degeneration **(large arrows)** and mitochondrial degeneration **(small arrow)**. Contraction bands seen in this specimen are also seen in biopsy specimens from normal hearts and thus are not considered a definite abnormality in endomyocardial biopsy tissue. (×7,333, reduced by 25 percent.)

microscopy. Definite myocyte degeneration was seen in the specimen of 4 (36 percent) of 11 patients (Fig. 2) and in 1 (10 percent) control subject. Definite mitochondrial degenerative changes, usually marked or severe, were recorded in all 11 specimens from the patients with mitral valve prolapse (Fig. 3). Mitochondrial abnormalities were noted in six control biopsy specimens, but these changes were generally of lesser severity (Fig. 4). Nuclear chromatin clumping and intracell edema were more prominent in the patients with prolapse.

Discussion

Cardiomyopathy in mitral valve prolapse: We found a high frequency rate of abnormalities including fibrosis, focal hypertrophy, myocyte and mitochrondrial degeneration, nuclear chromatin clumping and intracell edema in the endomyocardial biopsy specimens obtained from our patients with mitral valve prolapse. These biopsy findings favor the coexistence of a *myocardial* disease process in symptomatic patients with idiopathic mitral valve prolapse. The possibility that a cardiomyopathy is involved in mitral valve prolapse was first mentioned in 1966 by Hancock and Cohn,[7] and later investigators supplied indirect left ventriculographic evidence of a myocardial disorder.[10–13] However, no histologic evidence of a cardiomyopathy has been reported.

Limitations of study: Although our report lends support to the theory of a cardiomyopathy, we interpret our observations with caution for several reasons:

1. All 14 of our patients had symptoms troublesome enough to warrant investigation. All but one had significant chest pain, and most had cardiac conduction abnormalities and potentially serious cardiac arrhythmias. Thus, they were a highly selected group with mi-

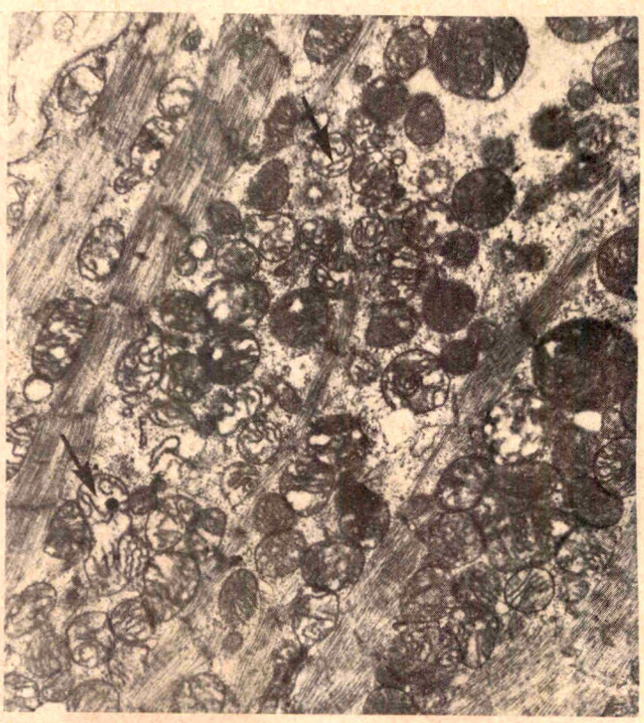


FIGURE 3. Patient 6. Electron micrograph showing severe mitochondrial degeneration with mitochondrial pleomorphism, mitochondrial swelling, cristolysis **(arrows)** and disruption of the outer membrane. (×12,500, reduced by 25 percent.)

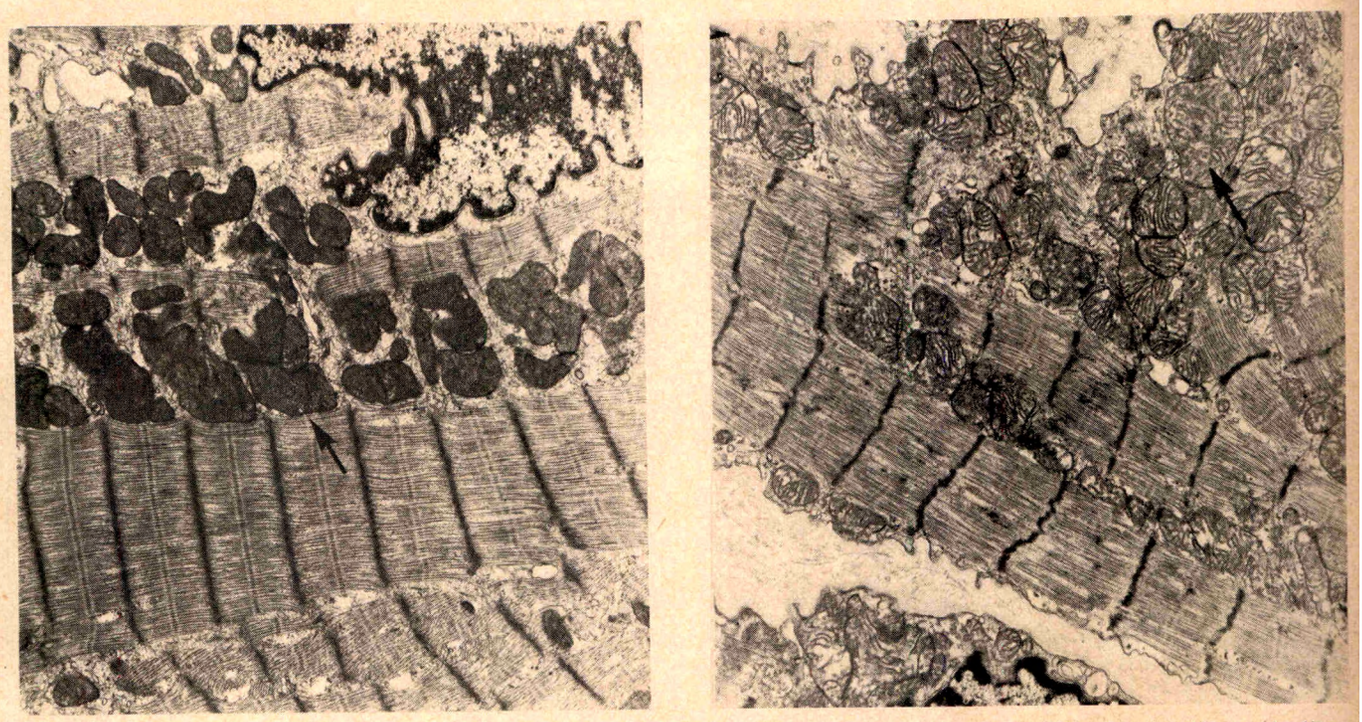


FIGURE 4. Left, control subject 5. Electron micrograph showing normal mitochondria with compact cristae **(arrow)**. The mitochondria are of uniform size and have organized, compact cristae. **Right,** control subject 6. Electron micrograph showing slight mitochondrial changes consisting of mild swelling and early cristal separation **(arrow)** graded questionably abnormal. (Both micrographs ×12,500, reduced by 25 percent.)

tral valve prolapse. Echocardiographic studies have demonstrated the remarkable frequency of mitral valve prolapse in apparently healthy subjects, and it is even relatively common to find combined echocardiographic and auscultatory findings indicative of this condition.[21,23,24] However, significant symptomatology is distinctly unusual; when symptoms are present, they are often vague and not severe enough to warrant invasive evaluation. Thus, conclusions drawn from our observations must be applied only to the relatively small proportion of patients with mitral valve prolapse who have prominent symptoms. In fact, because mitral valve prolapse is such a common "abnormality," one could speculate that our patients had coincidental mitral valve prolapse associated with independent cardiomyopathic processes. However, this latter possibility seems unlikely because chest pain is usually less prevalent in patients with cardiomyopathy than it was in our group and, in addition, all but one of our patients (Case 1) had normal heart size and left ventricular contractility, which are unusual findings in symptomatic subjects with idiopathic cardiomyopathy.

2. *Our method of establishing criteria for abnormality is another potential drawback of our study.* Because of an active cardiac transplantation program at this institution,[25] we are fortunate to have cardiac biopsy samples from normal hearts, obtained from cardiac donors. These samples are obtained by excision with a scalpel from the right ventricular septum of the donor heart, at the same site where endomyocardial biopsy specimens are obtained, after the heart has been arrested, cooled in iced saline solution and partially implanted in the recipient. This difference in the metabolic states of donor heart tissue and tissue obtained with the transvenous biopsy method in living patients would not alter the occurrence of fibrosis or myocyte hypertrophy; however, the electron microscopic abnormalities, especially the mitochondrial degenerative changes we found in control subjects, could have resulted from the cooling and protracted hypoxia to which the donor hearts were subjected.[26] If the latter were true, the difference between the mitochondria of patients and control subjects might have been even more striking than our findings indicate.

3. *The age difference between the donors and the patients with mitral valve prolapse is a third potential limitation of our study.* Because the majority of our donors were young, it is possible that the differences between this group and our patients with mitral valve prolapse may be due simply to age-related change. Although we cannot exclude this possibility, it should be noted that the two oldest donors, aged 37 and 44 years, respectively (Cases 8 and 10, Table II), had fewer changes noted on biopsy than the donor group as a whole, whereas the one patient with mitral valve prolapse who was under 20 years of age (Case 8) had one of the most abnormal biopsy specimens in the patient group. These observations argue strongly against age as an important source of the pathologic differences between the specimens of our control subjects and patient group.

4. *A fourth limitation is that we cannot be certain that tissue obtained from the right ventricular septum in these patients is representative of the entire heart.*

In using the right ventricular biopsy technique for histologic examination in patients with cardiomyopathy, we have found that the pathologic changes are generalized except in a few specific disease states (for example, focal myocarditis, pressure or volume overload of only one ventricle, localized radiation injury and endocardial fibrosis).

Pathologic findings in mitral valve prolapse: The two most distinct pathologic changes observed were fibrosis and mitochondrial degeneration, and these changes were dramatically different from control observations. Myocardial fibrosis is due to myocyte death followed by replacement with fibrotic tissue, except in those disorders in which idiopathic or drug-induced[27] fibrotic proliferation occurs. Mitochondrial degeneration is a nonspecific ultrastructural abnormality but usually accompanies more generalized deterioration of the cell. The mitochondrial dystrophy observed in all of our patients with prolapse may be the ultrastructural forerunner of the fibrosis.

The significance of intracell edema in our study group is undetermined. However, it suggests the presence of increased osmotically active particles within the cytoplasm, conceivably as a result of deterioration of intracell organelles, and is seen in other myocyte degenerative states.

The pathologic abnormalities in our patients with mitral valve prolapse are distinct, although relatively subtle. A myocardial disorder seems to be present in these patients, but it is not a severely destructive process that might be expected to lead regularly to advanced myocardial damage and failure. On the other hand, mild heart failure, arrhythmias and chest pain could arise from the type and severity of the pathologic changes we have reported.

Implications: We conclude that abnormalities of the myocytes as well as interstitial and endocardial fibrosis are present in some symptomatic patients with mitral valve prolapse. These changes may be indicative of a cardiomyopathic process and may account for arrhythmias, chest pain and some instances of congestive heart failure in these patients, but our data do not conclusively support this hypothesis.

Acknowledgment

We express our appreciation to R. L. Popp, MD and E. W. Hancock, MD for review of this manuscript, and to Marilyn Masek for technical assistance.

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Effect of Digoxin on Coronary Blood Flow and Myocardial Oxygen Consumption in Patients With Chronic Coronary Artery Disease

VOLKER KÖTTER, MD
KLAUS-PETER SCHÜREN, MD
ROLF SCHRÖDER, MD

Berlin, West Germany

In 10 patients with chronic coronary artery disease and without clinical evidence of congestive heart failure, the effects of 1.0 mg of digoxin intravenously on systemic hemodynamics, coronary blood flow, myocardial oxygen consumption and myocardial lactate extraction were studied both at rest and during atrial pacing. Atrial stimulation at a rate just below the threshold for angina led to a significant decrease in left ventricular end-diastolic pressure, from 10.6 ± 1.6 to 7.1 ± 0.8 mm Hg, associated with a significant decrease in left ventricular stroke work index per beat, from 76.7 ± 5.11 to 40.3 ± 4.01 g-m/m^2. After digoxin, nearly identical results in stroke work index could be observed at rest and during stimulation (75.2 ± 6.74 and 44.1 ± 5.92, respectively). However, left ventricular end-diastolic pressure decreased significantly before and during atrial stimulation (8.1 ± 1.29 and 4.7 ± 1.09 mm Hg, respectively). Cardiac index decreased from 3.08 ± 0.20 to 2.73 ± 0.17 liters/min per m^2 at rest but during pacing it no longer differed before and after digoxin (3.17 ± 0.22 and 3.10 ± 0.20 liters/min per m^2, respectively). Myocardial oxygen consumption and lactate extraction remained unchanged after digoxin both at rest and during atrial pacing.

It is concluded that some deficiency in left ventricular function is present in patients with chronic coronary artery disease even without clinical evidence of congestive heart failure. Digoxin improves left ventricular performance at rest and during stress conditions. An expected increase in myocardial oxygen consumption due to enhanced contractility is completely counterbalanced, probably by a decrease in left ventricular volume after digoxin.

The usefulness of digitalis in patients with chronic coronary artery disease without congestive heart failure is still debated. Malmborg et al.[1] reported favorable effects of a treatment with digitalis glycosides on the threshold for angina pectoris, whereas other investigators[2–5] found no influence of digitalis on the severity of angina.

Angina is caused by myocardial hypoxia due to an imbalance between oxygen supply and demand. It may occur whenever myocardial oxygen need increases. Thus a study directed primarily to the metabolic cost of digitalis, and to the changes in myocardial oxygen supply and demand in patients with chronic coronary artery disease, would obviously be important. Surprisingly, however, there are only a few studies on the acute effects of cardiac glycosides that include, in addition to hemodynamic data, measurements of coronary blood flow, myocardial oxygen consumption and myocardial lactate extraction in patients with coronary artery disease.[6,7] Moreover, these studies concern measurements under resting conditions only. In this study we investigated the effects of acute digitalization on myocardial oxygen consumption and myocardial lactate

From the Department of Cardiology and Pneumonology of the Medizinische Klinik und Poliklinik der Freien Universität Berlin, Hindenburgdamm 30, 1000 Berlin 45, Germany. Manuscript received March 10, 1978; revised manuscript received May 24, 1978, accepted May 24, 1978.

Address for reprints: Volker Kötter, MD, Klinikum Steglitz der Freien Universität Berlin, Medizinische Klinik und Poliklinik, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

extraction, relating the data to concurrent changes in hemodynamic determinants, both at rest and during atrial stimulation, in 10 patients with chronic coronary artery disease without congestive heart failure.

Method

Patients: Ten men, aged 32 to 65 years (average 48), who had a clinical history of angina pectoris and angiographic evidence of advanced coronary artery disease and were undergoing diagnostic cardiac catheterization were selected for the study. Four patients had a history of myocardial infarction. No patient had clinical or radiologic evidence of congestive heart failure. All patients had sinus rhythm and showed no dysrhythmia during atrial stimulation. Measurements were always made before diagnostic left ventriculography and selective coronary angiography. All patients were familiar with the nature of the procedure, and informed consent was obtained before the study was instituted.

Methods of investigation: Investigations were performed in the morning after a light breakfast. For the preceding 3 weeks no patient had been receiving digitalis. With use of the Seldinger technique and insertion through the femoral vein, a no. 7 Cournand catheter was inserted into the pulmonary artery, a no. 7 Goodale-Lubin catheter was passed into the coronary sinus and a bipolar stimulation catheter was positioned at the lateral wall of the right atrium. In addition, a no. 7 multipurpose catheter was introduced by way of the femoral artery into the thoracic aorta or the left ventricle. The catheters located in the coronary sinus and the intrathoracic aorta had identical total inner volumes.

Measurements: *Pressures* were recorded from the left ventricle, aorta, right ventricle, right atrium and pulmonary artery. End-diastolic pressures were measured by averaging 10 consecutive ventricular beats with the peak of the R wave in the electrocardiogram as the reference point. Pressures were recorded by means of Statham P23D strain gauges on a Hewlett-Packard photographic recorder, with mean pressure values determined by electronic integration. The common 0 reference level for all pressures was set at 5 cm below the sternal angle with the patient supine.

Cardiac output was determined in duplicate with the dye-dilution technique using indocyanine green. Cardiac index, stroke volume index, and systemic vascular resistance were computed with standard formulas.

The left ventricular stroke work index (SWI) in g-m/m^2 was calculated using the formula SWI = [SVI (SBP − LVEDP) × 13.6]/1,000, where SVI = stroke index in ml/m^2, SBP = systolic blood pressure in mm Hg and LVEDP = left ventricular end-diastolic pressure in mm Hg.

Coronary vascular resistance (mm Hg/ml/min × 100 g) was determined as the ratio between mean diastolic aortic pressure minus mean left ventricular diastolic pressure and coronary blood flow.

Blood samples for determination of lactate concentrations (Biochemica Testkombination, Boehringer, Mannheim, Germany) and oxygen content (Lex-O_2-Con, Lexington Instruments, Lexington, Massachusetts) were taken simultaneously from the coronary sinus and the aorta. Lactate concentrations were not analyzed in the first three patients in our study.

Coronary blood flow was measured using the argon method with gas-chromatographic analysis of argon in the arterial and coronary venous blood. Details of this method, which allows measurements of coronary blood flow up to 500 ml per minute × 100 g myocardial tissue, have previously been published.[8–12] Experiments in closed chest dogs have demonstrated the accuracy of the argon method for the whole range of coronary blood flow; simultaneous comparison of coronary blood flow as measured with the argon method and the Pitot tube principle resulted in a correlation coefficient of $r = 0.982$.[11] In accordance with our experience the reproducibility of a given argon concentration in blood assessed with gas chromatographic analysis is in the range of ±0.5 percent.[10] The tissue-blood partition coefficient of argon is 1.1. The gas mixture of 79 percent argon and 21 percent oxygen was applied through a tightly fitting mouthpiece with a unidirectional valve of low resistance; during a brief period of adaptation the patient breathed room air through this system. Then the argon-oxygen mixture was connected abruptly. At the same time the sampling of arterial and coronary venous blood, each in duplicate, was started with a special motor pump unit (Unita I, Braun, Melsungen, Germany). The sampling periods lasted 5 minutes in all cases. At the end of the saturation phase of 5 minutes another sample of arterial and coronary venous blood was taken. Determinations of the argon blood concentrations were performed with gas chromatography (trace gas analyzer 1533 B, Varian, Darmstadt, Germany) after extraction through a specially designed extraction chamber.[9] Calculation of coronary blood flow was performed according to the formula of Kety and Schmidt.[13]

Myocardial oxygen consumption ($M\dot{V}O_2$ in ml/min × 100 g) was determined as the product of coronary blood flow (ml/min × 100 g) and the arterial-coronary venous oxygen content difference (volumes percent).

Statistical analyses were performed using Student's t test with paired comparison. All values are mean values ± standard deviation of the mean value.

Procedure: After the first control measurement (C_1) was obtained, atrial stimulation (P_1) was started. The ventricular rate was slowly increased until mild angina developed. Pacing was continued at a rate just below the threshold for angina pectoris. Ten minutes later hemodynamic functions, coronary blood flow, oxygen content and lactate concentrations were measured. Then 1.0 mg of digoxin was slowly administered intravenously within 5 minutes. Thirty minutes later the same measurements were obtained before (C_2) and after atrial stimulation (P_2) at identical ventricular rates.

Results

Hemodynamics (Table I, Fig. 1): Except for slightly increased left ventricular end-diastolic pressure due to a high *A* wave in 4 of the 10 patients, all control hemodynamic values before administration of digoxin were within the normal range. During atrial stimulation (P_1) at a mean ventricular rate of 126/min, diastolic and mean aortic pressures increased distinctly, whereas left ventricular end-diastolic pressure decreased from 10.6 ± 1.6 to 7.1 ± 0.8 mm Hg. Cardiac output remained unchanged. As expected, left ventricular stroke work index decreased from 76.7 ± 5.1 to 40.3 ± 4.0 g-m/m^2.

After administration of digoxin at rest (C_2), left ventricular end-diastolic pressure decreased from 10.6 ± 1.6 to 8.1 ± 1.3 mm Hg. Pulmonary arterial mean and diastolic pressures decreased correspondingly. Right ventricular end-diastolic pressure and mean right atrial pressure also decreased significantly. Cardiac index decreased from 3.1 ± 0.2 to 2.7 ± 0.2 liters/min per m^2. Arterial pressure, stroke work index and heart rate showed no significant change. However, there was a small increase in systolic and mean aortic pressures.

During atrial stimulation after digitalization (P_2), left ventricular end-diastolic pressure decreased further

from 8.1 ± 1.29 to 4.7 ± 1.1 mm Hg, whereas the stroke work index was unaltered and cardiac index increased from 2.73 ± 0.17 to 3.1 ± 0.2 liters/min per m^2 (P <0.005). Thus, the cardiac index during atrial stimulation no longer differed before and after digoxin. The other hemodynamic functions remained unaffected by digoxin during stimulation.

Coronary blood flow myocardial oxygen consumption and lactate extraction (Table II, Fig. 2 and 3): *At rest* (C_1), coronary blood flow was 73.1 ± 5.4 ml/min × 100 g of myocardial tissue, and during pacing it increased to 95.8 ± 5.6 (P_1), whereas $M\dot{V}O_2$ increased from an average of 8.9 ± 0.7 to 11.8 ± 0.7 ml O_2/min × 100 g. At the same time, myocardial lactate extraction showed an insignificant decrease from 28.3 ± 4.7 to 20.8 ± 4.9 percent.

After digoxin, coronary blood flow decreased slightly, from 73.1 ± 5.4 to 68.4 ± 3.5 ml/min × 100 g at rest, whereas myocardial oxygen consumption was unchanged because of a corresponding increase in arterial-coronary venous oxygen content difference; lactate extraction was also unchanged.

During atrial stimulation values for myocardial oxygen consumption before and after digoxin were nearly identical. Coronary blood flow on the average was about 6 ml/min × 100 g lower after digoxin. Again there was a corresponding increase in arterial-coronary venous oxygen content, from 12.4 ± 0.5 to 13.2 ± 0.6 volumes percent. After digoxin, myocardial lactate extraction was somewhat decreased in five of seven patients during atrial stimulation; these differences, however, were not significant.

TABLE I

Hemodynamic Data in Patients With Angina Pectoris (mean ± standard error of the mean)

		Control		Digoxin
HR (min^{-1})	C_1	69.0 ± 2.69	C_2	66.8 ± 3.92
	P_1	125.9 ± 2.84‡	P_2	125.9 ± 2.84‡
SBP (mm Hg)	C_1	136.9 ± 7.31	C_2	144.0 ± 8.53
	P_1	139.7 ± 8.95	P_2	140.3 ± 9.84
DBP (mm Hg)	C_1	77.6 ± 3.97	C_2	79.4 ± 5.67
	P_1	97.5 ± 5.29‡	P_2	97.7 ± 0.73‡
MAP (mm Hg)	C_1	101.0 ± 4.59	C_2	104.6 ± 5.86
	P_1	117.2 ± 7.31‡	P_2	116.9 ± 8.15‡
LVEDP (mm Hg)	C_1	10.6 ± 1.6	C_2	8.1 ± 1.29*
	P_1	7.1 ± 0.8†	P_2	4.7 ± 1.09**†
CI (liters/min per m^2)	C_1	3.08 ± 0.20	C_2	2.73 ± 0.17*
	P_1	3.17 ± 0.22	P_2	3.10 ± 0.20‡
SVI (ml/m^2)	C_1	44.96 ± 2.68	C_2	41.70 ± 2.46
	P_1	25.46 ± 2.08‡	P_2	24.86 ± 1.83‡
PA_s (mm Hg)	C_1	22.9 ± 1.51	C_2	23.7 ± 1.31
	P_1	24.7 ± 2.44	P_2	19.1 ± 0.98
PA_d (mm Hg)	C_1	10.8 ± 1.53	C_2	7.7 ± 0.87
	P_1	13.0 ± 2.50‡	P_2	10.1 ± 1.26†
PA_m (mm Hg)	C_1	14.3 ± 1.42	C_2	12.0 ± 0.98**
	P_1	16.20 ± 2.34	P_2	12.2 ± 0.98**
RVEDP (mm Hg)	C_1	6.4 ± 0.73	C_2	4.7 ± 1.0*
	P_1	3.0 ± 0.78‡	P_2	2.6 ± 0.9‡
RA_m (mm Hg)	C_1	2.7 ± 0.59	C_2	1.20 ± 0.64**
	P_1	1.3 ± 0.57	P_2	1.5 ± 0.7
SWI (g-m/m^2)	C_1	76.7 ± 5.11	C_2	75.2 ± 6.74
	P_1	40.3 ± 4.01‡	P_2	44.1 ± 5.92‡
SVR (dyne sec/cm^{-5})	C_1	1451.2 ± 95.7	C_2	1689.1 ± 117.8**
	P_1	1652.8 ± 138.5‡	P_2	1656.2 ± 127.3

P (probability values): * <0.05 and ** <0.025 (comparisons before and after digoxin); † = <0.05 and ‡ <0.025 (comparisons of values during control conditions and with atrial stimulation).

C_1 and C_2 = control measurements before (C_1) and after (C_2) digoxin; CI = cardiac index; DBP = diastolic blood pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial blood pressure; P_1 and P_2 = atrial stimulation before (P_1) and after (P_2) digoxin; PA_d = diastolic pulmonary arterial pressure; PA_m = mean pulmonary arterial pressure; PA_s = systolic pulmonary arterial pressure; RA_m = right atrial mean pressure; RVEDP = right ventricular end-diastolic pressure; SBP = systolic blood pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index.

Discussion

Left ventricular function in coronary disease and the effect of digitalis: Mild deficiency in left ventricular function is present in many patients with chronic coronary disease without clinical evidence of left heart failure, and ventricular performance usually improves after digitalization.[1,3,4,6] In normal subjects left ventricular end-diastolic pressure after digoxin remains unchanged.[3] In our series, left ventricular end-diastolic

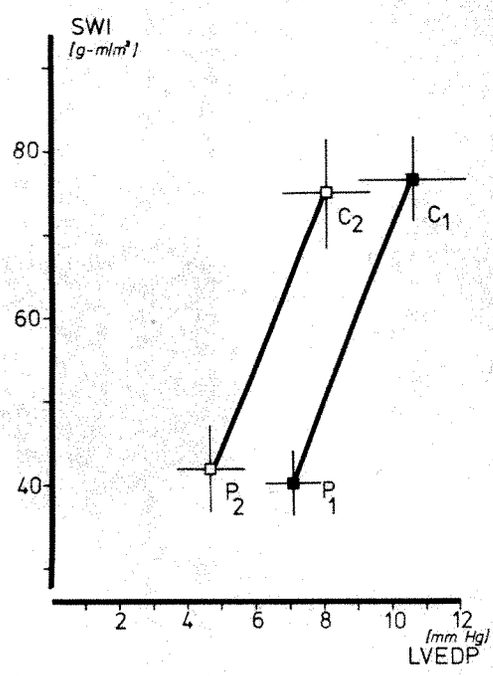


FIGURE 1. Effects of 1.0 mg of digoxin intravenously on the relation between left ventricular end-diastolic pressure (LVEDP) and left ventricular stroke work index (SWI) in 10 patients with coronary artery disease before and during atrial stimulation. C_1 and C_2 = control measurements before (C_1) and after (C_2) digoxin administration. P_1 and P_2 = atrial stimulation before (P_1) and after (P_2) digoxin.

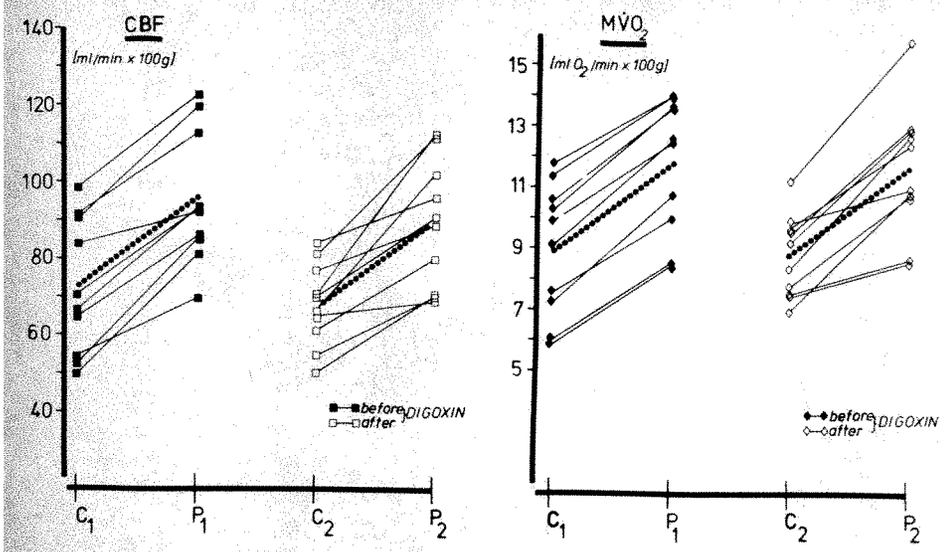


FIGURE 2. Effect of 1.0 mg of digoxin intravenously on coronary blood flow (CBF) and myocardial oxygen consumption ($M\dot{V}O_2$) in 10 patients with coronary artery disease. Abbreviations as in Figure 1.

pressure decreased significantly, from 10.6 to 8.1 mm Hg. A similar decrease in patients with coronary heart disease has been reported,[1,3,6] even though left ventricular end-diastolic pressure was within normal limits. Also, in our study during atrial stimulation and in other studies during exercise,[3,4] left ventricular end-diastolic pressure was decreased by digitalis glycosides.

During atrial stimulation in normal subjects Parker et al.[14] found a decline in stroke volume and in left ventricular stroke work per beat of approximately 40 percent, but no change in cardiac index; in accordance with the Starling relation, left ventricular end-diastolic pressure decreased. In contrast, left ventricular end-diastolic pressure did not decrease in patients with angina pectoris, in spite of a similar decrease in left ventricular stroke work during pacing. In our patients atrial stimulation at a rate just below the threshold for angina led to a comparable decrease in left ventricular stroke work index per beat of 47 percent, but this decrease was associated with a significant decrease in left ventricular end-diastolic pressure, from 10.6 to 7.1 mm Hg. After digoxin, values for stroke work index were nearly identical at rest and during atrial stimulation; however, left ventricular end-diastolic pressure decreased significantly before and during atrial stimulation. These findings indicate a shift of the left ventricular function curve to the left (Fig. 1) and thus suggest that mild deficiency in left ventricular performance is present in patients with coronary artery disease who have no clinical evidence of left heart failure.

TABLE II

Metabolic Data in Patients With Angina Pectoris (mean ± standard error of the mean)

		Control		Digoxin
CBF (ml/min × 100 g)	C_1	73.08 ± 5.38	C_2	68.44 ± 3.52
	P_1	95.82 ± 5.58‡	P_2	89.79 ± 5.21‡
(a − cs) DO_2 (vol %)	C_1	12.23 ± 0.49	C_2	12.92 ± 0.41
	P_1	12.38 ± 0.52	P_2	13.18 ± 0.63**
CVR (units)	C_1	1.10 ± 0.08	C_2	1.19 ± 0.12
	P_1	1.06 ± 0.11	P_2	1.14 ± 0.13
$M\dot{V}O$ (ml^2O_2/min × 100 g)	C_1	8.93 ± 0.71	C_2	8.77 ± 0.43
	P_1	11.79 ± 0.71‡	P_2	11.72 ± 0.69‡
Lactate (%)	C_1	28.3 ± 4.7	C_2	29.5 ± 4.23
	P_1	20.8 ± 4.9	P_2	14.85 ± 4.9‡

** Probability (P) value <0.025 (comparisons before and after digoxin).

‡ P value 0.025 (comparison of values during control conditions and with atrial stimulation).

(a-cs) DO_2 = arterio-coronary-sinus oxygen difference; CBF = coronary blood flow; CVR = coronary vascular resistance; lactate = myocardial lactate extraction; $M\dot{V}O_2$ = myocardial oxygen consumption.

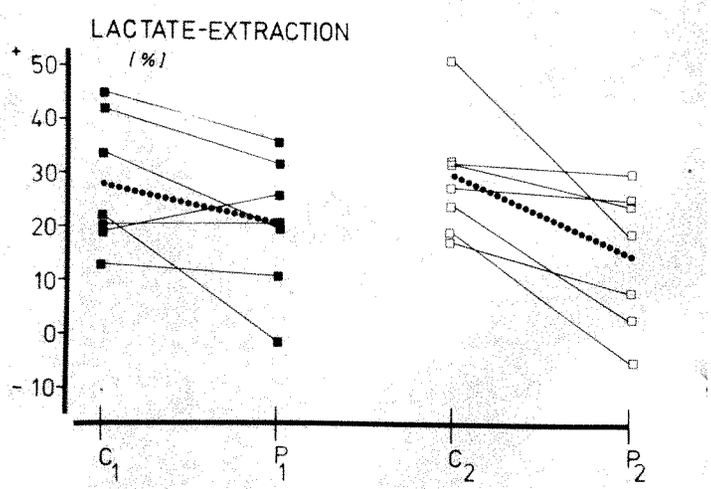


FIGURE 3. Effect of 1.0 mg of digoxin on myocardial lactate extraction in seven patients with coronary artery disease. Abbreviations as in Figure 1.

Myocardial oxygen demand and coronary blood flow in coronary disease and the effect of digitalis: The salutary hemodynamic effects of digitalis must be considered in relation to its effects on myocardial oxygen demand. In coronary artery disease without congestive heart failure digoxin may impose an undesirable metabolic cost upon the myocardium. Acetyl strophanthidin given to canine preparations without heart failure resulted in increased myocardial oxygen consumption.[15] However, in preparations with a failing heart, no change in myocardial oxygen consumption occurred; the increase in myocardial oxygen consumption caused by an enhanced contractile state was completely counterbalanced by diminished wall tension due to decreased ventricular volume.[15]

Epicardial electrocardiographic mapping in small experimental myocardial infarcts demonstrated an increase of ischemic injury with administration of ouabain.[16] When the extent and severity of ischemic injury were enlarged substantially by occlusion of the left anterior descending coronary artery near its origin with consecutive hemodynamic deterioration, digoxin did not increase ischemic injury.[17]

The inotropic properties of digitalis glycosides improve the contractile state in the normal[18–23] and the failing heart.[23–25] However, contractility is a major determinant of myocardial oxygen consumption.[26] An increase in myocardial oxygen consumption can be anticipated unless other simultaneous changes prevent its occurrence. The significant decrease in left ventricular end-diastolic pressure after digitalization in patients with coronary artery disease without clinical evidence of left ventricular failure suggests a decrease in end-diastolic volume. De Mots et al.[6] and Vogel et al.[27] found a decrease in left ventricular volume in these patients after ouabain. At the same time left ventricular ejection fraction increased.[27] This decrease in ventricular volume and thus, wall tension, could prevent or at least diminish an increase in oxygen demand caused by improved contractility.

In our study there was no difference in myocardial oxygen consumption before and after digoxin either at rest or during atrial pacing. The same results at rest were obtained by De Mots et al.,[6] and Tauchert et al.[7] Investigations on myocardial oxygen consumption during definite stress conditions in patients with chronic coronary artery disease before and after digitalization have not previously been reported. The argon method we used requires maintenance of a steady state for at least 16 minutes. Because this prerequisite could not be fulfilled during ergometric exercise, atrial pacing was chosen as the stress technique. It is an advantage of this method that heart rate is kept constant because heart rate itself is an important determinant of contractility and myocardial oxygen consumption. However, a disadvantage of the technique is that it provides an unphysiologic form of work load. Nevertheless, we believe that this technique provides meaningful data with regard to coronary blood flow and myocardial oxygen consumption at rest and during stress. In this and in other comparable studies in patients with chronic artery disease, digitalization did not provoke any increase in myocardial oxygen consumption. We consider a decrease in ventricular volume a possible way of preventing an increase in oxygen demand in such patients.

Nearly identical results on coronary blood flow and myocardial oxygen consumption at rest were obtained by Tauchert et al.[7] Using the xenon-133 technique, De Mots et al.[6] attained substantially higher values for coronary blood flow. Because of comparable arterial-coronary venous oxygen differences a higher value for myocardial oxygen consumption was also computed. The xenon-133 technique requires homogeneity in the distribution of blood flow, a prerequisite that certainly is not met in patients with coronary artery disease. Klocke et al.[28] have shown that the xenon technique tends to overestimate coronary blood flow, presumably because the coronary sinus effluent more closely reflects the areas of better perfused myocardium. The argon technique overcomes most of these technical problems in measurements, even if there still is no completely satisfactory technique for the estimation of coronary blood flow in man.[29]

De Mots et al.[6] observed a decrease in arterial pressure after administration of ouabain. They considered this decrease responsible for the lack of the expected increase in oxygen consumption due to increased contractility after administration of the drug. However, clinical and experimental data indicate that the application of digitalis glycosides should result in an increase or at least in no change in arterial pressure. In the series of De Mots et al.[6] the preceding left ventriculography may explain the findings of lower arterial pressure after the subsequent administration of digitalis. In our study, we found some increase in systolic and mean arterial pressures, although the change was not significant. Independent from variations in arterial pressure, the myocardial oxygen consumption remained unchanged after digoxin.

Coronary and systemic vascular resistance after digitalis: In our series both systemic and coronary vascular resistance levels increased slightly after digoxin. Experimental data suggest a direct constricting effect of digitalis glycosides on arterial smooth muscle.[19,30–33] These increases in coronary and systemic vascular resistances do occur when digitalis glycosides are given over a short injection time[30]; in our investigations digoxin was given over a period of 5 minutes. A 15 minute infusion of ouabain caused no significant changes in mean arterial pressure or systemic vascular resistance.[30] The increase of vascular resistance within the coronary vessels as well as in other vascular beds is probably explained by this direct vascular glycoside effect. Garan et al.[34] found evidence that the central nervous system is a major site of action of digitalis in producing neurogenic vasoconstriction in coronary vasculature.

Myocardial lactate extraction after digoxin Myocardial lactate extraction was not significantly different before and after digoxin either at rest or during atrial stimulation. At rest, lactate extraction remained

within the normal range[35] of more than 8 percent in all patients. During atrial stimulation three patients had a lactate value of less than 8 percent, one patient before and two patients after digoxin. In one patient lactate extraction decreased from 22.5 to 1.6 percent before and from 19.4 to 5.3 percent after digoxin. In another it decreased from 13.2 to 11.4 percent during the first stimulation and from 23.9 to 3.3 percent after digoxin. The difference between control and pacing lactate extraction values was not significantly greater after digoxin (−7.5 percent before and −14.5 percent after digoxin, $P > 0.05$). Thus, abnormal lactate metabolism as an index of myocardial anaerobiosis did not occur as the consequence of digitalization.

These findings are in keeping with the results of De Mots et al.[6] However, care must be exercised in applying these data to regional myocardial perfusion and metabolism. Although the average lactate extraction does not change, regional areas of metabolic deterioration may be compensated for by improved metabolism elsewhere in the heart. However, after digitalization no patient had angina pectoris at a pacing rate just below the threshold for angina as determined before application of digoxin. Therefore, probably no increase in regional myocardial ischemia was present. The conclusions are in agreement with data on the effects of digitalis on myocardial perfusion, as measured from thallium-201 uptake. In a recently published study[36] on patients with coronary artery disease and left ventricular dysfunction, chronic digoxin administration improved myocardial perfusion and reversed a hand-grip-induced regional myocardial hypoperfusion.

Therapeutic indications: In all previously reported studies digitalis has not produced an increase in myocardial oxygen consumption or resulted in deterioration in the clinical symptoms of angina. Furthermore, some improvement in effort tolerance either was found[1] or was possibly not detected because of the special conditions of the experimental setting.[3] Thus it seems reasonable to us to give digitalis to those patients with coronary artery disease without evidence of congestive heart failure who exhibit limited exercise tolerance possibly caused by decreased cardiac contractile reserve. Despite its beneficial effects on left ventricular performance, digitalization did not consistently alter the level of exercise tolerance at which angina occurs.[2–5] Thus, digitalis is not an antianginal agent. The target of the therapeutic approach is left ventricular insufficiency, often the consequence of chronic coronary artery disease.

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Effects of Digitalis on Atrial Vulnerability

TOBY R. ENGEL, MD, FACC
ANA DEL C. GONZALEZ, MD

Philadelphia, Pennsylvania

The effects of digitalis on vulnerability to atrial fibrillation and flutter were assessed in man, using the model of repetitive atrial firing initiated by post-drive atrial extrastimulation. Nine patients without heart failure or significant mitral valve disease were tested before and 30 minutes after the administration of 0.01 mg/kg ouabain. When repetitive firing was manifested by flutter, neither the flutter cycle length nor the interval from the initiating beat to the first flutter beat was consistently altered by ouabain. Repetitive firing was found at the atrial site with the shortest functional refractory period. The vulnerable zone bordered this refractory period. The functional refractory period was lengthened after ouabain, from 231 ± 13 to 246 ± 15 msec (mean ± standard error of the mean) ($P < 0.025$). Partly because of prolonged refractoriness, the vulnerable zone was curtailed by ouabain, from 32.2 ± 5.7 to 9.4 ± 4.6 msec ($P < 0.001$). This result suggests a protective effect of digitalis against atrial fibrillation and flutter independent of its hemodynamic actions.

After almost two centuries of investigation, the electrophysiologic effects of digitalis on atrial fibrillation and flutter remain incompletely defined, in part because of the multifactorial action of digitalis: on the cell membrane, autonomic control, baroreceptor sensitivity, vasculature, contractility and ventricular rate. Thus it is difficult to determine why a change from one rhythm to another is associated with the administration of digitalis. In addition, there are discrepancies in the data from animals[1–3] and patients,[4–6] presumably because the nervous system modulates action of the drug.[7]

This investigation was performed to ascertain the effect of digitalis on *vulnerability* to atrial fibrillation and flutter. We studied patients free of valvular heart disease and congestive heart failure in order to minimize hemodynamic effects. We used repetitive firing[8] initiated by atrial extrastimulation as a model for fibrillation and flutter so that patients could be studied during sinus rhythm, thereby minimizing hemodynamic, autonomic and electrophysiologic effects of changes in heart rate.

Material and Methods

Patient population: The 9 study patients were chosen from a consecutive series of 13 patients exhibiting vulnerability to atrial fibrillation or flutter during electrophysiologic testing. These nine patients were selected for evaluation of digitalis because the induced arrhythmias were not sustained, thus allowing complete evaluation before and after drug administration. Although all patients had symptoms consistent with atrial tachyarrhythmia, many did not have recorded episodes of spontaneous tachycardia (Table I). Spontaneous atrial fibrillation and flutter were more frequent in patients excluded from study because of sustained induced arrhythmias.

None of the study patients had clinical evidence of congestive heart failure, mitral stenosis or hemodynamically significant mitral regurgitation. None had right atrial enlargement as judged from fluoroscopy or echocardiographic evidence of left atrial enlargement or major elevation of left ventricular end-diastolic

From the Cardiovascular Division, The Medical College of Pennsylvania, Philadelphia, Pennsylvania. This study was supported in part by a grant from the American Heart Association, Southeastern Pennsylvania Chapter, Philadelphia, Pennsylvania. This work was performed during Dr. Engel's tenure as a Career Development Investigator of that chapter and while Dr. Gonzalez was a recipient of a grant from the American Heart Association, Commonwealth of Puerto Rico Chapter, San Juan, Puerto Rico. Manuscript received March 21, 1978; revised manuscript received June 6, 1978, accepted June 7, 1978.

Address for reprints: Toby R. Engel, MD, The Medical College of Pennsylvania, 3300 Henry Avenue, Philadelphia, Pennsylvania 19129.

TABLE I

Clinical Features of Patients Receiving Ouabain

Case no.	Age & Sex (yr)	Anatomic Diagnosis	Spontaneous Arrhythmias	Heart Rate (beats/min)	SART (msec)	SACT (msec)	LVEDP (mm Hg)	Echo-cardiogram
1	31M	MVP	Undefined tachy	86	940	110	16	MVP, normal LA
2	35M	Normal	None	68	1070	50	14	. . .
3	27M	MVP	None	65	920	70	15	Normal
4	51M	CHD	None	92	820	63	14	. . .
5	61M	Normal	Parox A Fib	91	780	66	. . .	Normal
6	64F	Normal	Parox A Fib	75	980	51	. . .	Normal
7	35M	Normal	Parox A Fib	67	1240	99	. . .	Normal
8	50M	Normal	Atrial bigeminy	55	1460	110	. . .	Normal
9	50M	Normal	Atrial tachy	67	1090	81	. . .	Normal

CHD = coronary heart disease; LA = left atrium; LVEDP = left ventricular end-diastolic pressure; MVP = mitral valve prolapse; Parox A Fib = paroxysmal atrial fibrillation; SACT = sinoatrial conduction time, expressed as $(A_2\text{-}A_3\text{–}A_1\text{-}A_1)/2$; SART = sinoatrial recovery time; tachy = tachycardia.

pressure when these variables were assessed (Table I). No patient had recorded asystole; all had normal sinoatrial conduction time, normal sinoatrial recovery time and equivalent pauses after cessation of induced fibrillation or flutter.

Stimulation and recording techniques: Atrial extrastimulation was performed in the postabsorptive state after informed written consent had been obtained. Cardioactive medication had not been received for at least 3 days. Generally a quadripolar catheter with an interelectrode distance of 1 cm was passed to the right atrium, and the distal electrode pair was used for atrial stimulation. In two patients separate bipolar catheters were used. Rectangular 2 msec stimuli at twice threshold were provided by a Grass S88 stimulator, using SIU5 isolation units.

Extrastimuli were applied at coupling intervals of 5 to 10 msec, as digitally programmed with an electrically isolated Quartec APS-3C controller. Extrastimuli were first applied during sinus rhythm and then after more than eight beats of constant atrial pacing or drive. Drive was terminated with the extrastimulus, and only single extrastimuli were applied.

TABLE II

Refractory Periods of Right Atrial Sites Tested

Case no.	Cycle Length Tested (msec)	Functional Refractory Period (msec) High	Mid	Low
1	Sinus rhythm 684	290	. . .	290*
	Atrial drive 650	300	. . .	230*
2	Sinus rhythm 933	320	310	300
	Atrial drive 480	270	270	200*
3	Sinus rhythm 855	270	. . .	. . .
	Atrial drive 480	170*	. . .	. . .
4	Sinus rhythm 650	240*	. . .	. . .
	Atrial drive 480	220*	. . .	. . .
5	Sinus rhythm 666	330	. . .	280
	Atrial drive 480	280	. . .	210*
6	Sinus rhythm 820	250*	. . .	230
	Atrial drive 480	240*	. . .	240
7	Sinus rhythm 950	335	340	330
	Atrial drive 480	335	235*	330
8	Sinus rhythm 1110	. . .	510	. . .
	Atrial drive 480	. . .	280*	. . .
9	Sinus rhythm 920	315	. . .	. . .
	Atrial drive 480	290*	. . .	. . .

* Repetitive atrial firing was initiated at this site.

Extrastimulation was first performed with the stimulating catheter positioned at the high lateral right atrium. If atrial fibrillation or flutter did not result, the low or mid (lateral or septal) atrium was tested (Table II). When these secondary sites were used, the threshold was redetermined at each new site.

Coupling intervals and the characteristics of atrial firing were determined from bipolar recordings, using the proximal electrode pair of the quadripolar catheter. Wenckebach atrioventricular (A-V) conduction never occurred during atrial drive, and the records were carefully inspected to exclude the possibility of atrial echoes initiating atrial firing. In two patients recordings were made from a separate bipolar catheter at least 1 cm from the stimulating site. Atrial and His bundle recordings were made at a paper speed of 100 mm/sec with filter settings of 30 to 500 hertz using an Electronics for Medicine DR-12 oscilloscopic recorder. Surface leads I, II, aVF and V_1 were simultaneously recorded.

Definition of terms: *Atrial flutter* was diagnosed if, after the last sinus or driven beat (A_1) and the applied extra beat (A_2), discrete flutter waves were recorded in surface leads, and more than three discrete atrial depolarizations with a cycle length of less than 250 msec were recorded from the atrial lead (Fig. 1).

Atrial fibrillation was diagnosed if disorganized atrial activity lasting longer than 1 second followed A_2 as recorded in both surface and atrial leads (Fig. 2). In eight patients, when disorganized atrial activity was recorded it followed both the extrastimulus and A_2, allowing measurement of the A_1-A_2 interval initiating fibrillation. In one patient, A_2 was considered the onset of disorganized atrial activity.

The vulnerable zone was the range of A_1-A_2 intervals, as measured from the atrial electrogram, resulting in atrial fibrillation or flutter (Fig. 2).

The atrial functional refractory period was the shortest A_1-A_2 interval attained (in the atrial electrogram). *The effective refractory period* was the longest S_1-S_2 interval not resulting in a propagated response to S_2 (not resulting in A_2). The cycle length of flutter was averaged from the recordings in the atrial electrogram (A_3), using the 4 to 10 depolarizations after the first initiated beat, depending on their duration. The interval A_2-A_3 represented the time from the applied premature beat to the first initiated beat (Fig. 1).

Protocol for digitalization: After control determination of the vulnerable zone and functional refractory period, the patient was allowed to return to sinus rhythm. Ouabain, 0.01 mg/kg body weight, was infused for 5 minutes. Thirty minutes after completion of the infusion, stimulation at the site originally used to initiate fibrillation or flutter was again performed. The strength of the stimulus was not changed, and

the cycle length used for atrial drive was the same as that used before the administration of ouabain. No patient had persistent atrial fibrillation or flutter on testing after the administration of ouabain.

Results were expressed as mean ± standard error of the mean. Statistical comparisons were made with a paired *t* test.

Results

Vulnerable zone: A zone of vulnerability to repetitive atrial firing, with induction of atrial fibrillation or flutter, was evident during sinus rhythm in three of nine patients. When heart rate was accelerated by atrial drive, a vulnerable zone was found in all nine patients before and in eight patients after



FIGURE 1. Initiation of atrial flutter. S_1 and A_1 refer, respectively, to the stimulus artifact and the atrial depolarization of atrial drive (cycle length 480 msec, 120 beats/min). The extrastimulus S_2 results in a premature beat (A_1-A_2 = 280 msec). At this coupling interval there is an early extra beat recorded first from the higher atrium (A_2-A_3 = 290 msec). The subsequent atrial rhythm is diagnosed as flutter because of discrete depolarizations with a cycle length of less than 250 msec recorded in the right atrial electrogram (AE) and His bundle electrogram (HBE) and because of discrete flutter waves recorded in surface leads II, aVF and V_1.

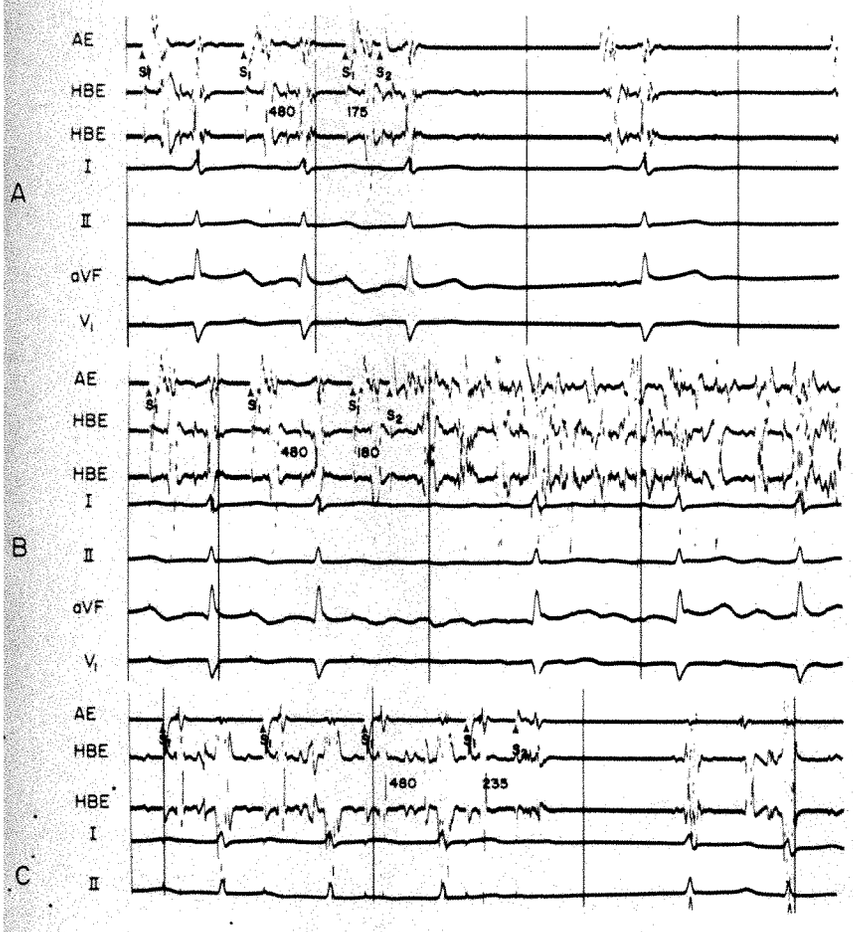


FIGURE 2. Initiation of atrial fibrillation by extrastimulation within the vulnerable zone. S_1 indicates the stimulus artifact of atrial pacing or drive (cycle length 480 msec, 120 beats/min). S_2 indicates the extrastimulus. **Panel A** shows the longest S_1-S_2 interval (175 msec) at which S_2 fails to propagate and result in atrial depolarization (effective refractory period). **Panel B** shows a 5 msec increment in S_1-S_2 (180 msec) that results in a propagated response to S_2. The repetitive atrial firing that is initiated is considered to be atrial fibrillation because of (1) continuous activity recorded in the atrial electrogram (AE) and His bundle electrograms (HBE), and (2) disorganized atrial activity recorded in surface leads. Similar repetitive atrial activity was initiated within an S_1-S_2 range of 180 to 230 msec. **Panel C** shows that with an S_1-S_2 interval of 235 msec or greater there is only a single propagated response to S_2. (The gain has been reduced in the atrial electrogram and enhanced in the His bundle electrogram in panel C.) Refractoriness and the vulnerable zone were measured in terms of the propagated responses (A_1-A_2; see text).

TABLE III

Effect of Ouabain (0.01 mg/kg) on Atrial Vulnerability at Constant Atrial Drive Rate

Case no.	Functional Refractory Period (msec)		Vulnerable Zone (msec)		Flutter Cycle Length (msec)		A_2-A_3 (msec)	
	Control	Ouabain	Control	Ouabain	Control	Ouabain	Control	Ouabain
1	230	240	230–280	240–280	215	217	205	200
2	200	200	200–210	200 only	184	210	170	160
3	170	210	170–210	210 only	181	199	220	260
4	220	220	220–250	220 only	190	180	160	160
5	210	220	210–240	220–240	...	...	...	...
6	240	250	240–280	250–265	245	240	230	210
7	235	230	240 only	240 only	191	188	200	200
8	280	320	280–330	None	248	...	270	...
9	290	320	290–330	320–330	...	256	...	260
Mean	231	246	32.2	9.4	201*	206*	198*	198*
SEM	13	15	5.7	4.6	10.1	8.7	11.2	15.1
P	<0.025		<0.001		NS*		NS*	

* Patients 5, 8 and 9 not included.
NS = not significant; *P* = probability; SEM = standard error of the mean.

the administration of ouabain. The vulnerable zone bordered the functional refractory period when cycle length was kept constant by atrial drive, except for a gap of 5 to 10 msec in Patient 7 (Table III).

In five patients extrastimulation at more than one site was required before a site was discovered at which repetitive firing could be induced. Table II indicates that repetitive atrial firing was found at the site with the shortest refractory period. In fact, except for Patient 6, the functional refractory period of sites at which repetitive firing was not evident exceeded the outer margin of the vulnerable zone determined at the susceptible site.

Effect of ouabain on vulnerable zone and atrial refractory period: Table III lists the data obtained from the vulnerable site when the heart rate was kept constant by pacing. The atrial functional refractory period increased in six of nine patients after the administration of ouabain. The average functional refractory period increased from 231 ± 13 to 246 ± 15 msec (P <0.025). Similarly, the atrial effective refractory period increased from 184 ± 11 to 198 ± 15 msec (P <0.05). The duration of the vulnerable zone was shorter after the administration of ouabain in eight patients; there was no change in the remaining patient, who had a zone that was initially very narrow. Overall, the duration of the vulnerable zone decreased from 32.2 ± 5.7 to 9.4 ± 4.6 msec (P <0.001).

Similar results were obtained during sinus rhythm, despite the changed cycle length after the administration of ouabain and beat to beat variation in the cycle length preceding the extrastimulus. The functional refractory period was never shortened by ouabain. In three patients repetitive atrial firing was induced during sinus rhythm, and the duration of the vulnerable zone decreased from 23.3 ± 6.7 to 15.0 ± 12.6 msec.

No consistent reason was found for the narrowing of the vulnerable zone. Figure 3 shows that in six patients a prolonged functional refractory period at least partly explained the narrowing. However, the outer margin of the zone was shortened in four patients. In two patients the functional refractory period was unchanged, and the zone was narrowed only because the outer margin occurred earlier.

Effect of ouabain on atrial flutter and fibrillation: When repetitive firing was manifested by flutter, the cycle length of the flutter decreased after the administration of ouabain in three patients and increased in three other patients

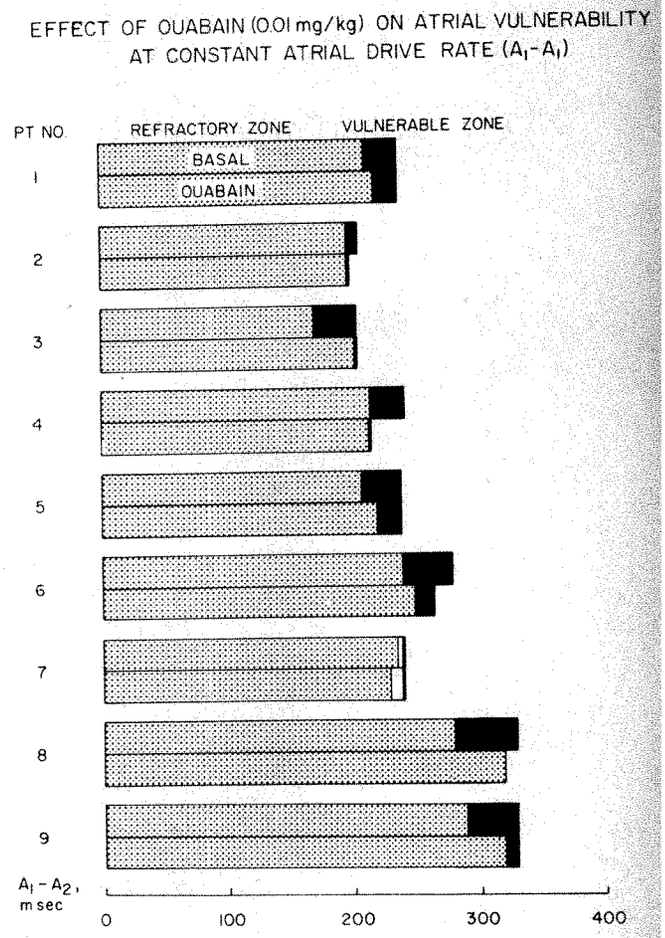


FIGURE 3. Refractory and vulnerable zones before and after the administration of ouabain. Heart rate was constant. To the right of the bars, atrial extrastimulation caused only single propagated responses. The **stippled areas** represent the portion of the atrial cycle refractory to extrastimulation and indicate that the functional refractory period was not shortened by ouabain. The **solid areas** represent the zones vulnerable to rapid atrial firing. Vulnerable zones were curtailed after the administration of ouabain (P <0.001), in some patients (PT) because the functional refractory period was later in diastole (Patients 1, 3, 5, 6, 8 and 9), and in others because the outer margin of the zone was earlier (Patients 2, 4, 6 and 8).

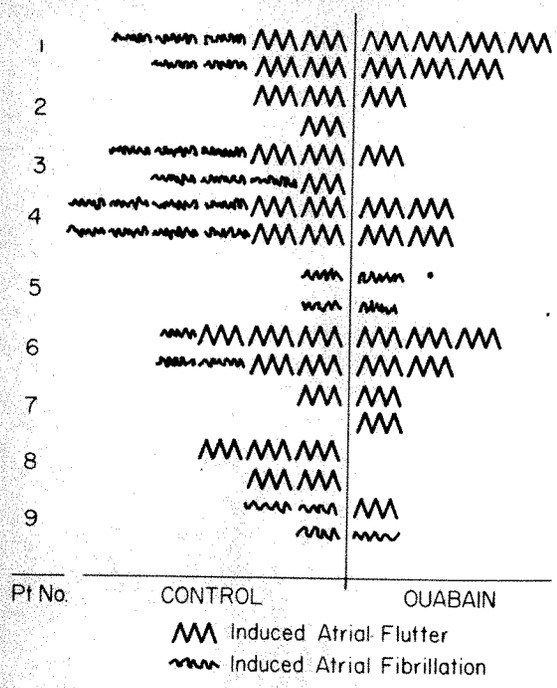


FIGURE 4. Individual instances of repetitive atrial firing encountered in this study are depicted as **saw-toothed symbols** (atrial flutter) or **wavy lines** (atrial fibrillation). The lesser number of events after ouabain reflects less frequent testing for vulnerability as well as narrowed vulnerable zones. However, atrial fibrillation appears to occur less often after the administration of ouabain; instead vulnerability is more frequently manifested as atrial flutter. Pt = patient.

(Table III). The average change, from 201 ± 10 to 206 ± 9 msec, was not significant. Similarly, the average interval from the applied premature beat to the first flutter depolarization (the A_2-A_3 interval) was unchanged (from 198 ± 11 to 198 ± 15 msec). There was generally a fixed cycle length of flutter after the first A_3, both before and after the administration of ouabain. Thus, ouabain did not induce a "rhythm of development" as occurs in tachycardias triggered from afterpotentials.[9] Furthermore, the length of A_2-A_3 was sometimes shorter than the length of the subsequent cycle (A_3-A_3), which would not be expected if the first A_3 was triggered from an early afterpotential.

Figure 4 depicts the individual instances of repetitive atrial firing observed in this study. The saw-toothed symbols indicate atrial flutter, and the wavy lines atrial fibrillation. The total number of episodes of repetitive firing before and after the administration of ouabain reflects the number of times each patient was tested. This number does not indicate that ouabain reduced the incidence of arrhythmias, but it does suggest that ouabain enhanced the likelihood of atrial flutter where previously atrial fibrillation might have occurred. Specifically, fibrillation was induced in six patients before but in only two patients after the administration of ouabain.

Discussion

Genesis of atrial fibrillation and flutter: Atrial fibrillation and flutter are spontaneously initiated only by very premature atrial ectopic complexes.[10,11] The critical timing of the ectopic complex defines a zone in which susceptible atria are vulnerable to fibrillation and flutter. Discovery of a vulnerable zone does not define the mechanism of arrhythmogenesis; for example, critically timed premature beats initiate tachycardias based on threshold after depolarizations as well as reentry.[9] However, the identification of a vulnerable zone does offer a key to the reproduction of atrial fibrillation and flutter using the atrial extrastimulus technique. This method was first carefully described in animals by Andrus et al.[12] and in patients by Haft et al.[13] Bigger and Goldreyer[14] distinguished the vulnerable zone from the echo zone for the initiation of paroxysmal supraventricular tachycardia. Sung et al.[15] used the techniques to investigate the genesis of atrial fibrillation and flutter in the Wolff-Parkinson-White syndrome. Calon et al.[16] in a preliminary report, used this model to describe the effects of quinidine on atrial fibrillation. Thus far, there has been no complete survey of the clinical relevance of demonstrating atrial vulnerability. It is used in this study only as a model to assess the effect of drugs on atrial fibrillation and flutter.

Wyndham et al.[8] studied the effect of heart rate on vulnerability to atrial fibrillation and flutter. A vulnerable zone was not encountered in most of their patients at normal heart rates. At faster heart rates (atrial drive), the functional refractory period was earlier, exposing the vulnerable zone for the first time. These results emphasize the need to define the effect of therapeutic maneuvers on the relation between the vulnerable zone and the refractory period.

Relation of vulnerable zone to refractory period: Our results confirm the observation of Wyndham et al.[8] that the vulnerable zone borders the functional refractory period. We too found that vulnerability may be obscured at longer *atrial cycle lengths.* When refractoriness was curtailed at shorter cycle lengths, the vulnerable zone was evident. In addition, our data suggest that vulnerability may be obscured *at certain atrial sites.* When other atrial sites with shorter refractory periods were stimulated, the vulnerable zone was evident. The common denominator is a short functional refractory period.

Our results do not indicate whether vulnerable sites show repetitive firing because their refractory periods are very early (curtailed by atrial pacing or a focal abnormality) or very different (dispersion of refractoriness). In our study, once a vulnerable site was discovered, the catheter was not moved, so that the effect of the drug could be determined more precisely. Assessment of whether vulnerable sites were sites of unusually curtailed or disparate refractoriness will require another study.

Effects of ouabain on functional refractory period: Data on the effects of digitalis on atrial refractoriness in animal preparations are not consistent with data thus far obtained in patients. Refractory periods are prolonged in isolated atria.[17,18] Lewis[1] argued that vagal effects would predominate if the nervous system was intact, with shortening of refractory periods, but he provided no data. The issue appears to have been settled by the frequently quoted study of Mendez and Mendez.[2] Digitalis prolonged the atrial refractory period in the denervated canine preparation but decreased the

atrial refractory period in anesthetized dogs when vagal innervation was left intact.

However, vagal drive does not appear to shorten the atrial refractory period in unanesthetized patients because atropine does not produce a consistent effect in man[19–21]; in one study, atropine actually shortened atrial refractory periods.[22] This may explain in part why Wu et al.[5] found no effect of ouabain on atrial refractoriness in patients studied for paroxysmal supraventricular tachycardia and why Goodman et al.[23] found no significant effect of digoxin, even in the denervated hearts of patients after cardiac transplantation. Dhingra et al.[4] found that ouabain actually prolonged atrial refractoriness in normal subjects. The results of our study confirm that digitalis does not shorten the atrial refractory period in man. In fact, the functional refractory period, determined from atrial sites that were selected for curtailed refractoriness to begin with, actually lengthened after the administration of ouabain.

Effects of ouabain on the vulnerable zone: It is traditionally believed that digitalis converts atrial flutter to atrial fibrillation and that sinus rhythm results from the withdrawal of digitalis.[24] However, as reviewed by Jennings et al.,[25] there is a wide difference of opinion about the frequency with which digitalis will convert atrial fibrillation to sinus rhythm. Furthermore, Luckey[26] reported a 46 percent frequency of conversion of atrial flutter to sinus rhythm with digitalis. The effects of digitalis on the conversion of atrial fibrillation and flutter to sinus rhythm are controversial and inconsistent, in part because control of heart failure and ventricular rate may be presumed to play a role in determining the rhythm in some patients.[25,27] Because worsening heart failure and atrial disease are uncontrolled variables, there is no clear-cut evidence of the action of digitalis in maintaining sinus rhythm, once it has been established.

In the patients in our study, the effects of digitalis on hemodynamics and heart rate were minimized. Consistent abbreviation of the vulnerable zone for the initiation of atrial fibrillation and flutter after the administration of ouabain suggests that the electrophysiologic effects of digitalis protect against these arrhythmias, although the effects of the drug are slight. Mainly, the vulnerable zone was narrowed because ouabain slightly prolonged refractoriness at the vulnerable site, obscuring a portion of the zone. However, the outer margin of the zone was shortened in some patients. If we assume that the outer margin of the vulnerable zone represents the refractory period of a unidirectionally blocked pathway, then these results raise the possibility that digitalis minimizes disparities of atrial refractoriness. This thesis is consistent with a failure of digitalis to slow conduction consistently (see later).

The narrowed vulnerable zone suggests that in some patients digitalis alone might be sufficient to reduce the frequency of atrial fibrillation and flutter when they are paroxysmal. At least, the likelihood that a spontaneous atrial premature beat would have the critical timing necessary to initiate arrhythmia is reduced.

Other effects of ouabain: The acceleration of atrial conduction in flutter would be manifested by a shorter flutter cycle length if there was a reentrant circuit. Also, atrial decompression from the treatment of heart failure would result in a shorter flutter cycle length. This could lead to interruption of the flutter, the leading edge of the excitation wave finding a site of still refractory atrium, resulting in sinus rhythm or fractionation of the excitation wave and conversion to fibrillation. However, in dogs digitalis slows atrial conduction, even during vagal stimulation.[3] When the vagi are intact, digitalis slows the rate of atrial flutter and often converts flutter to fibrillation.[24,28]

We previously reported[6] that ouabain caused no change in atrial conduction, as manifested by the P-A interval, in patients with the sick sinus syndrome. In a preliminary report, Leier et al.[29] found no change in the P-A or interatrial interval after the administration of ouabain. Dhingra et al.[4] found that ouabain lengthened the P-A interval in normal subjects. However, the P-A interval is not completely relevant to the conduction interval of an atrial reentrant circuit for several reasons: (1) Digitalis could change the site of exit of the impulse from the sinus node; (2) the P-A interval could reflect changes in specialized fibers; and (3) P-A conduction does not reflect the actual pathway of the postulated reentrant loop. We assessed atrial conduction during flutter using cycle length and also the interval to first reappearance of depolarization at the site recording the extrastimulus, and we found no consistent effect of ouabain. Although there often seemed to be a slowing before termination, there was no "warm-up phase" or "rhythm of development" at the onset of flutter, either before or after the administration of ouabain. This last observation can be considered very tentative evidence that there was reentry before and after the administration of ouabain, rather than automaticity or triggering to threshold of oscillatory afterpotentials.[9,30]

Clinical implications: In contrast to some reports,[24,26–28] in our study atrial flutter was almost invariably initiated after the administration of ouabain, whereas atrial fibrillation was frequently initiated before digitalization (Fig. 4). These findings suggest the possibility that if there is a propensity to atrial fibrillation or flutter, the arrhythmias would be more likely to occur in the form of flutter when they occur paroxysmally in the digitalized patient. We are aware of no clinical correlate of this observation, which should be investigated to determine the potential disadvantage of long-term administration of digitalis for paroxysmal atrial fibrillation.

This investigation of repetitive atrial firing in patients suggests that digitalis does not shorten the atrial refractory period and that it has an inconsistent effect on atrial conduction. The vulnerable zone for the initiation of atrial fibrillation and flutter was abbreviated, suggesting a protective effect of digitalis against these arrhythmias.

Acknowledgment

We thank Charlotte Sweeney and her assistants for expert technical assistance and Rachel Chatburn for careful preparation of the manuscript.

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Pulmonary Pulsus Alternans in Acute Myocardial Infarction

JOSÉ LOPEZ-SENDON, MD
ISABEL COMA-CANELLA, MD
LUIS MARTIN JADRAQUE, MD
ISIDORO GONZALEZ MAQUEDA, MD

Madrid, Spain

A total of 100 consecutive patients with acute myocardial infarction were studied with hemodynamic monitoring. Five groups were established: A, all eight patients with pulmonary pulsus alternans; B, the four patients in group A who did not die; C, the four patients in group A who died in the coronary care unit; D, control patients with heart failure, but without pulmonary alternans; and E, patients in group A who underwent hemodynamic studies just before (five patients) the appearance of pulmonary pulsus alternans and six patients studied just after its disappearance.

Patients in group A had a smaller cardiac index ($2P < 0.005$), stroke index ($2P < 0.05$), left ventricular stroke work index ($2P < 0.01$) and higher pulmonary resistance levels ($2P < 0.005$) than patients in control group D. They also had a smaller cardiac index ($2P < 0.005$) and higher pulmonary resistance ($2P < 0.05$) levels than patients in group E. Patients in group B had a higher stroke index ($2P < 0.05$), left ventricular stroke work index and left ventricular net work index ($2P < 0.01$) than patients in group C. Appearance of pulmonary pulsus alternans accompanied a decrease in cardiac index and an increase in pulmonary pressure and resistance levels. Its disappearance sometimes followed a drug-induced decrease in pulmonary pressure and resistance levels, and an increase in cardiac index. On other occasions it occurred after the administration of inotropic agents (digoxin or dopamine), without changes in pulmonary pressure.

Pulmonary pulsus alternans in acute myocardial infarction may appear under two conditions: (1) right ventricular strain secondary to left heart failure; and (2) impaired right ventricular contractility. Mortality was greater in group A than in group D ($2P < 0.05$). Patients in group C were in worse condition than those in group B. Therefore, the prognosis depends on the degree of heart failure and not on the pulmonary pulsus alternans itself.

Mechanical (pulsus) alternans is in most cases an index of ventricular failure.[1–5] It is a frequent finding in various heart diseases, including aortic stenosis,[3,4,6,7] cardiomyopathies[2,6,8] and chronic ischemic heart disease.[6,8] The alternans in pulmonary pressure is a less frequent finding than systemic alternans.[3,9] It was first described in detail by Rabago et al.[10] in a patient with an interatrial septal defect, and later by Ferrer et al.[1] in several cases of mitral stenosis and heart failure. In several studies it was related to pulmonary embolism,[9] cardiomyopathies[19] and other causes of right ventricular strain.[1,9,11,12] At the same time, it was demonstrated that mechanical alternans does not necessarily occur simultaneously in both the systemic and pulmonary circulations.[1,2,8,13]

We have not found any reference to pulmonary pulsus alternans in acute myocardial infarction. In this report we present the clinical and hemodynamic significance of this condition, as well as the cause of its appearance and its prognostic value during acute myocardial infarction.

From the Coronary Care Unit, Department of Medicine, Residencia Sanitaria La Paz, Universidad Autónoma de Madrid, Madrid, Spain. Manuscript received March 16, 1978; revised manuscript received May 30, 1978, accepted May 31, 1978.

Address for reprints: José Lopez-Sendon, MD, C. Juan Ramon Jimenez 2, 4° B, Madrid 16, Spain.

TABLE I

Clinical and Hemodynamic Evolution in Eight Patients With Pulmonary Pulsus Alternans

Case no.	PPA	PTP	CI	TPR	Clinical Subset	Hemodynamic Subset	Drugs
1	Yes	48-32/25-15	2.7	800	C-II	H-II	...
	No	22/13	3.0	427	C-II	H-I	Nitroglycerin
2	Yes	44-36/27	1.9	1137	C-II	H-IV	...
	Yes	37-33/18	2.3	835	C-II	H-II	Phentolamine
	No	26/15	3.2	475	C-I	H-I	Phentolamine
3	Yes	63-49/36-31	2.1	1600	C-II	H-IV	...
	Yes	48-42/23-20	2.5	864	C-II	H-II	Nitroprusside
	Yes	59-51/27-23	1.7	1647	C-II	H-IV	Nitroprusside
	No	49/22	2.7	918	C-II	H-II	Dopamine + nitroprusside
	Yes	50-47/24	2.1	1226	C-II	H-IV	Isosorbide dinitrate
	Yes	40-36/20	2.4	867	C-II	H-II	Isosorbide dinitrate + digoxin
	No	43/20	2.9	763	C-II	H-II	Isosorbide dinitrate + digoxin
4	No	50/30	2.8	1057	C-II	H-II	...
	Yes	47-43/23	2.3	1043	C-II	H-II	Isosorbide dinitrate
	No	40/20	2.4	900	C-II	H-II	Isosorbide dinitrate + digoxin
5*†	Yes	67-63/35	2.0	1800	C-II	H-IV	...
	No	60/30	2.1	1524	C-II	H-IV	Dopamine
6*†	No	45/28	2.5	1073	C-II	H-II	...
	Yes	49-39/30/23	1.6	1634	C-IV	H-IV	Phentolamine
	Yes	38-32/21-19	2.2	909	C-IV	H-II	Dopamine + phentolamine
	Yes	43-37/28-26	2.3	1078	C-IV	H-II	Dopamine + phentolamine
	Yes	58-38/31-27	1.5	1884	C-IV	H-IV	Phentolamine
	Yes	45-35/22-18	1.7	1271	C-IV	H-IV	Phentolamine
	Yes	53-47/30-26	1.6	1750	C-IV	H-IV	Phentolamine + dopamine
	Yes	57-51/29	1.7	1756	C-IV	H-IV	Dopamine
	No	48/33	1.8	1689	C-IV	H-IV	Dopamine (large doses)
7*	No	46/27	1.8	1467	C-II	H-IV	...
	Yes	52-48/33	1.5	2028	C-IV	H-IV	Dopamine
8*†	No	45/30	2.4	1167	C-IV	H-II	...
	Yes	30-24/19-17	1.9	884	C-IV	H-IV	Nitroglycerin

* Patient died.
† Autopsy performed.
CI = cardiac index (liters/min per m^2); PPA = pulmonary pulsus alternans; PTP = pulmonary trunk pressure (mm Hg); TPR = total pulmonary resistance (dynes sec cm^{-5}/m^2).

Materials and Methods

Patients: Between August 1 and December 23, 1977, a total of 120 patients with acute myocardial infarction were admitted to the "La Paz" coronary care unit. Hemodynamic monitoring was performed in 100 of these patients. It was not performed for a variety of reasons in the remaining 20 patients, but none of these showed clinical heart failure or low cardiac output.

The diagnosis of acute myocardial infarction was determined using well known clinical, electrocardiographic and laboratory criteria.[14] All of the patients were admitted within the first 24 hours of evolution.

In each patient we studied the clinical features, classifying the patients according to Forrester's method[15] in the following subsets:

C-I: no evidence of pulmonary congestion or peripheral hypoperfusion.

C-II: pulmonary congestion only.

C-III: hypoperfusion only.

C-IV: both pulmonary congestion and hypoperfusion.

Hemodynamic data: Right heart catheterization was performed on admission by inserting a Swan-Ganz thermodilution catheter into the pulmonary trunk through the right antecubital vein. Right atrial, pulmonary arterial and pulmonary capillary wedge pressures were recorded through a Hewlett-Packard 1280 transducer, with a Siemens Elema Mingograph 34, at a paper speed of 25 mm/sec. Cardiac output was determined with the thermodilution technique, using an Edwards 9500 computer. In every case, at least three successive determinations were made, and the average value was calculated.

We followed Forrester's method,[15] classifying the hemodynamic studies in four subsets:

H-I: pulmonary capillary wedge pressure 18 mm Hg or less and cardiac index 2.2 liters/min per m^2 or greater.

H-II: pulmonary capillary wedge pressure more than 18 mm Hg and cardiac index more than 2.2 liters/min per m^2.

H-III: pulmonary capillary wedge pressure 18 mm Hg or less and cardiac index 2.2 liters/min per m^2 or less.

H-IV: pulmonary capillary wedge pressure more than 18 mm Hg and cardiac index 2.2 liters/min per m^2 or less.

Arterial blood pressure was measured with an arm cuff and expressed in mm Hg. Hemodynamic values were calculated according to the following formulas[16,17]: CI = CO/BSA, where CI is cardiac index in liters/min per m^2, CO is cardiac output in liters/min and BSA is body surface area in m^2; SI = CI/HR, where SI is stroke index in ml/beat per m^2 and HR is heart rate in beats/min; TPR = 80 (PTP/CI), where TPR is total pulmonary resistance in dynes sec cm^{-5}/m^2, 80 is the conversion

TABLE II

Values (mean ± standard deviation) for All Hemodynamic Variables in Every Group and Statistical Significance of Differences Between Groups

	Group A (19 studies)	Group B (9 studies)	Group C (10 studies)	Group D (30 studies)	Group E (11 studies)	2P values A vs. D	A vs. E	B vs. C
HR	85.1 ± 17.5	80.1 ± 17.8	90.0 ± 17.1	86.6 ± 16	87.9 ± 16.0	NS	NS	NS
PTP	31.5 ± 6.4	30.3 ± 5.8	32.6 ± 7.0	30.4 ± 7.3	29.7 ± 7.3	NS	NS	NS
PCP	23.4 ± 4.3	20.8 ± 7.3	24.9 ± 4.0	23.9 ± 4.0	20.7 ± 5.6	NS	NS	NS
RAP	11 ± 6.6	8.8 ± 7.0	13.0 ± 5.3	9.6 ± 4.06	8.5 ± 5.1	NS	NS	NS
BP	77.8 ± 16.6	85.1 ± 13.7	75 ± 17.8	90.3 ± 15.9	79.5 ± 15.7	0.025	NS	NS
CI	2.04 ± 0.36	2.17 ± 0.31	1.92 ± 0.42	2.62 ± 0.63	2.5 ± 0.5	0.005	0.005	0.05
SI	24.8 ± 5.8	28.2 ± 6.7	21.9 ± 2.5	31.1 ± 10.9	29.2 ± 8.2	0.05	NS	0.05
TPR	1319 ± 424	1113 ± 324	1505 ± 432	927 ± 245	1041 ± 428	0.005	0.05	NS
LVSWI	31.5 ± 10.7	38.6 ± 11.1	25.2 ± 5.3	45.7 ± 18.8	36.1 ± 13.4	0.01	NS	0.01
LVNWI	24.7 ± 11	31.9 ± 11.4	18.3 ± 5.5	36.0 ± 16.3	28.0 ± 13.5	0.02	NS	0.01
LVNWI/LVSWI	0.76 ± 0.10	0.81 ± 0.1	0.71 ± 0.08	0.78 ± 0.06	0.75 ± 0.08	NS	NS	0.01
RVNWI	9.9 ± 3.7	12.2 ± 2.5	7.8 ± 3.3	13.2 ± 4.1	11.6 ± 3.2	NS	NS	NS

BP = blood pressure (mm Hg); CI = cardiac index (liters/min per m^2); HR = heart rate (beats/min); LVNWI = left ventricular net work index (g-m/beat per m^2); LVSWI = left ventricular stroke work index (g-m/beat per m^2); PCP = mean pulmonary capillary pressure (mg Hg); PTP = mean pulmonary trunk pressure (mm Hg); RAP = right atrial pressure (mm Hg); RVNWI = right ventricular net work index (g-m/beat per m^2); SI = stroke index (ml/beat per m^2); SWI = stroke work index (g-m/beat per m^2); TPR = total pulmonary resistance (dynes sec cm^{-5}/m^2).

factor to dynes sec cm^{-5} and $\overline{PTP}$ is mean pulmonary trunk pressure in mm Hg; LVSWI = SI × $\overline{ASP}$ × 0.0136, where LVSWI is left ventricular stroke work index in g-m/beat per m^2, $\overline{ASP}$ is mean aortic systolic pressure in mm Hg and 0.0136 the conversion factor from mm Hg/ml to g; $\overline{ASP}$ = 0.8 (aortic systolic − aortic diastolic) + aortic diastolic pressure; LVNWI = SI ($\overline{ASP}$ − $\overline{PCP}$) × 0.0136, where LVNWI is left ventricular net work index in g-m/beat per m^2 and $\overline{PCP}$ is mean pulmonary capillary pressure in mm Hg; LVNWI/LVSWI; RVNWI = SI ($\overline{PSTP}$ − $\overline{RAP}$) × 0.0136, where RVNWI is right ventricular net work index in g-m/beat per m^2, $\overline{RAP}$ is mean right atrial pressure in mm Hg and $\overline{PSTP}$ is mean pulmonary systolic trunk pressure.

Pulmonary pulsus alternans: This was defined as the alternation of strong and weak peak systolic pulmonary pressure in the presence of regular rhythm and in the absence of respiratory movements. We excluded patients with pulmonary pulsus alternans who also had the following: (1) valve disease (one patient with aortic stenosis); (2) major arrhythmias (two patients with ventricular tachycardia); or (3) false pulmonary pulsus alternans, such as the alternans that may accompany significant variations in rhythm, or is induced by atrial contractions in cases of external cardiac pacing or atrioventricular dissociation.

We found eight patients with pulmonary pulsus alternans. Their age was 62.2 ± 10.7 years (mean ± standard deviation). None had chronic obstructive lung disease. *The following groups were established:*

Group A: all eight patients with pulmonary pulsus alternans. From their studies we selected 19 different hemodynamic studies in which pulmonary alternans was present. These were separated by a minimal interval of 12 hours and showed significant changes in some of the measured values.

Group B: the four patients in group A who did not die in the coronary care unit (nine hemodynamic studies).

Group C: the four patients in group A who died while in the coronary care unit (10 hemodynamic studies).

Group D: control group of patients with 30 hemodynamic studies chosen at random from all patients without pulmonary alternans but included in subsets H-II and H-IV of Forrester's classification.

Group E: patients in group A who had hemodynamic measurements just before the appearance (five patients) or just after the disappearance (six patients) of pulmonary pulsus alternans (total of 11 hemodynamic studies).

We statistically compared the mean values of each hemodynamic measurement in groups A and D, A and E, and B and C, using Students' t test ($2P$ values).

Results

Clinical data: All eight patients with pulmonary pulsus alternans had clinical left heart failure (Table I). Six patients were in clinical subset C-II and two in C-IV. Five patients had clinical right heart failure, and one of them had pulmonary thromboembolism.

Hemodynamic data (Tables I and II): All 19 hemodynamic studies in group A (eight patients) showed pulmonary capillary pressure greater than 18 mm Hg; 12 studies were classified in subset H-IV and 7 in subset H-II. Patients in group A had lower values for blood pressure ($2P < 0.025$), cardiac index ($2P < 0.005$), stroke index ($2P < 0.05$), left ventricular stroke work index ($2P < 0.01$) and left ventricular net work index ($2P < 0.02$) and higher values for total pulmonary resistance ($2P < 0.005$) than patients in group D (control). Patients in group A had statistically smaller values for cardiac index ($2P < 0.005$) and higher values for pulmonary resistance ($2P < 0.05$) than patients in group E. When comparing group B (nonfatal pulmonary pulsus alternans) with group C (fatal pulmonary pulsus alternans) we observed that group B had higher values for stroke index ($2P < 0.05$), left ventricular stroke work index (LVSWI) ($2P < 0.01$) and left ventricular net work index (LVNWI) ($2P < 0.01$). The ratio LVNWI/LVSWI was smaller in group C ($2P < 0.01$).

The more interesting data for each hemodynamic study in group A are shown in Table I, as well as the hemodynamic data and clinical classification before the appearance of pulmonary alternans and after its disappearance (Group E), if available. In five patients the pulmonary trunk pressure and cardiac index were known before the pulmonary alternans was present. Note that pulmonary trunk pressure may be increased

or decreased when pulmonary alternans appears, but cardiac index always decreases and total pulmonary resistance usually increases (Fig. 1).

The disappearance of pulmonary pulsus alternans could be studied in six patients, including four with clinical improvement. The changes associated with the disappearance of pulmonary pulsus alternans were less striking than those that accompanied the appearance of pulmonary alternans but generally included a more or less important decrease in pulmonary trunk pressure and total pulmonary resistance (Fig. 2) or an increase in cardiac index, or both (Fig. 3). In four patients the pulmonary alternans disappeared after the administration of inotropic drugs such as dopamine or digoxin, with or without significant changes in pulmonary trunk pressure and cardiac index (Fig. 1 and 3). In three other patients pulmonary alternans disappeared after treatment with several vasodilators, which produced an important reduction in total pulmonary resistance values (Fig. 2).

Mortality: Four patients with pulmonary pulsus alternans died in the coronary care unit (group C) (Table I)—two with cardiogenic shock (H-IV) and two with pulmonary edema (H-II). Postmortem studies, performed in three of these patients revealed ischemic lesions in both ventricles of all three. The mortality rate was higher in patients with pulmonary alternans than in the patients of control group D with left heart failure (16.7 percent) ($2P < 0.05$).

Discussion

Incidence: Mechanical alternans of the lesser circulation simultaneous with or independent of left heart alternans occurs in patients with isolated left heart diseases and heart failure,[1] or primary right heart diseases such as idiopathic pulmonary hypertension[11] or

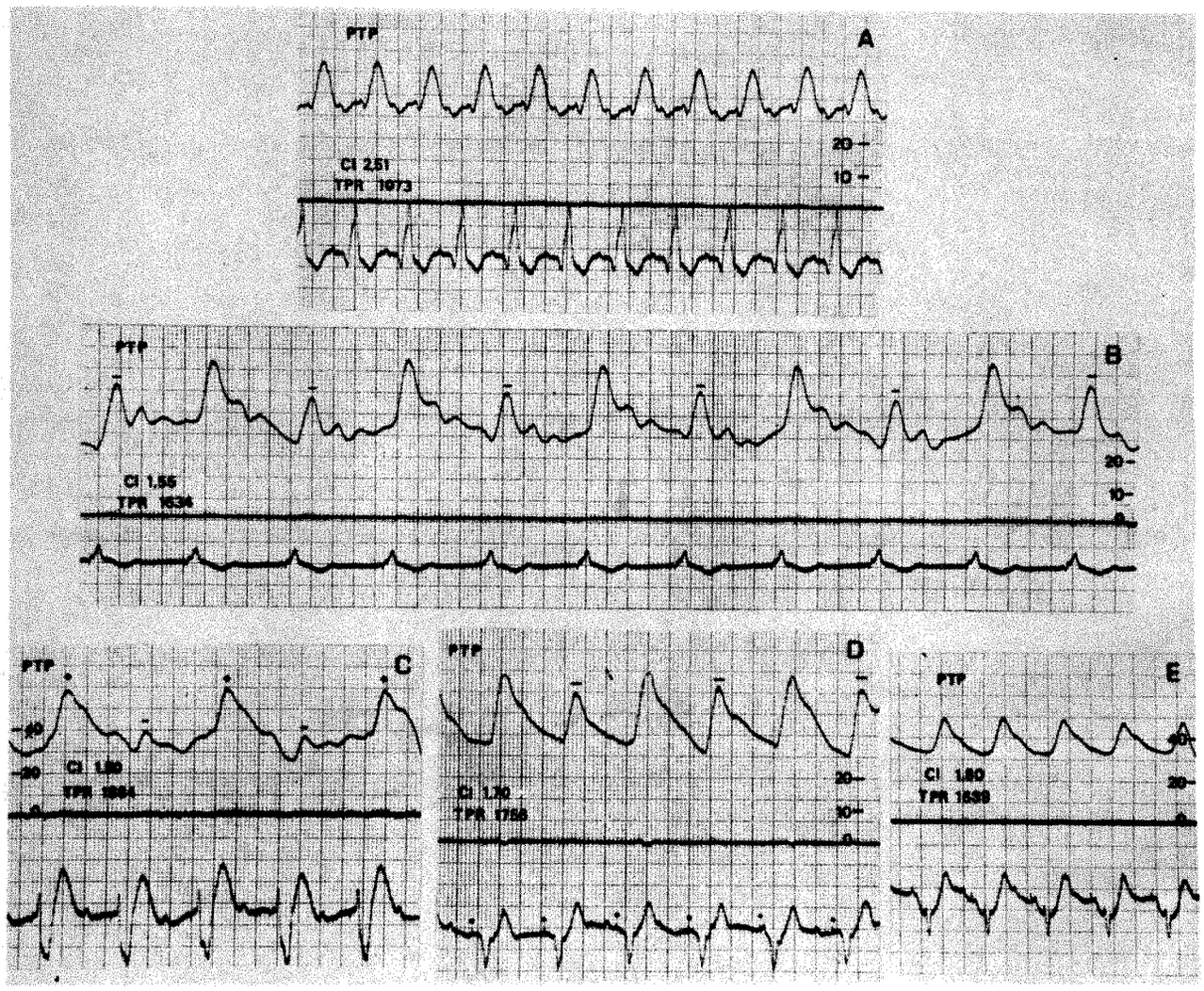


FIGURE 1. Case 6. Pulmonary alternans appears in **B** and is maximum in **C**, after an increase in total pulmonary resistance (TPR) and a decrease in cardiac index, with the same pulmonary trunk pressure (PTP). After administration of dopamine, pulmonary alternans diminishes in **D** and even disappears with high doses of dopamine (**E**). The patient had cardiogenic shock after the appearance of pulmonary alternans. CI = cardiac index (liters/min per m^2); PTP = pulmonary trunk pressure in mm Hg; TPR = total pulmonary resistance (dynes sec cm^{-5}/m^2).

pulmonary embolism.[9] Sometimes the underlying disease is common to both ventricles, as in cardiomyopathies.[2] Pulmonary pulsus alternans has been reported in patients with chronic ischemic heart disease[6,8] but not during acute myocardial infarction. The hemodynamic monitoring performed in almost all of our patients with acute myocardial infarction has proved that it is a frequent finding, appearing in at least 8 percent of patients.

Clinical and hemodynamic significance: Every patient with pulmonary pulsus alternans showed clinical, radiologic and hemodynamic signs of left heart failure. This failure was more severe than in patients without pulmonary alternans, documented by the lower values for cardiac index, stroke index, stroke work index and net work index. These findings are in agreement with previous data[1–5] associating mechanical alternans with heart failure. Even if it is possible to find mechanical alternans in people without heart disease, it occurs only in nonphysiologic conditions such as during arrhythmias or pacing at high rates.[4,13,18,20]

Significance during acute myocardial infarction: Two main mechanisms have been proposed to explain mechanical alternans: (1) the hemodynamic theory, based on Starling's principle, which holds that alternation in diastolic volume or pressure or fiber length accounted for the alternating contractile force (increase preload preceding the more powerful beats[7,19,21,22]); and (2) the myocardial theory, which holds that primary alternation in contractility of the whole or only part of the heart occurs in the absence of changes in ventricular diastolic volume.[6,8,18,23,25] We believe that mechanical alternans of the pulmonary pressure in acute myocardial infarction may appear under certain conditions:

1. Right ventricular strain secondary to left heart failure. A common finding in our patients with pulmonary pulsus alternans was severe left heart failure. It produced an increase in pulmonary resistance levels with corresponding overload to the right ventricle, with or without signs of right ventricular failure. Total pulmonary resistance levels were higher in these patients than in those without alternans. In many patients, the appearance and disappearance of pulmonary alternans followed significant changes in hemodynamic measurements (pulmonary trunk pressure, cardiac index and total pulmonary resistance values). These changes were due to the intervention of preload- or afterload-reducing agents without direct inotropic action.

Pulmonary pulsus alternans has been found in patients with primary pulmonary hypertension,[11] pul-

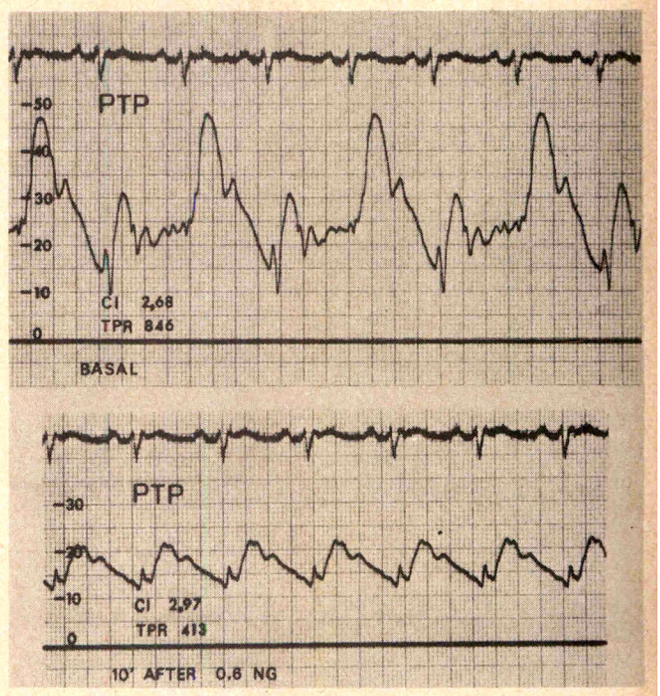


FIGURE 2. Case 1. Pulmonary pulsus alternans disappears 10 minutes after the sublingual administration of 0.6 mg of nitroglycerin (NG), with striking reduction in pulmonary pressures (PTP) and total pulmonary resistance (TPR). Abbreviations and units as in Figure 1.

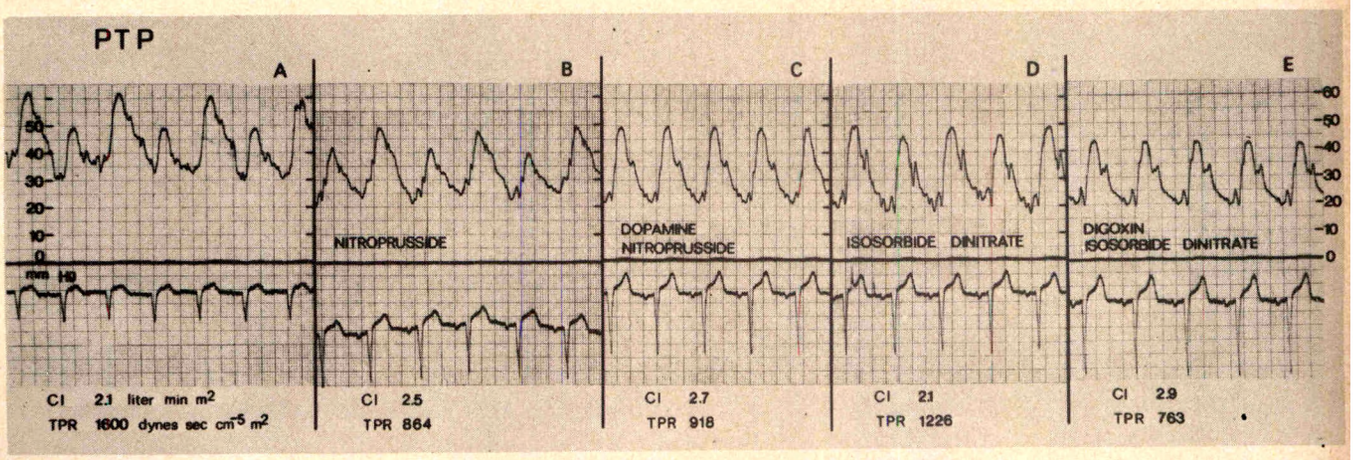


FIGURE 3. Case 3. Pulmonary pulsus alternans (**A**) does not disappear after reduction of pulmonary pressure and resistance with nitroprusside (**B**) until dopamine is administered (**C**). Alternans appears again when the inotropic drug is discontinued (**D**) and is no longer present when the patient is given intravenous digoxin. Note that pulmonary trunk pressure is the same in magnitude from **B** to **E**. Abbreviations and units as in Figure 1.

monary thromboembolism,[5] as well as in patients with valve disease.[1,12] In every case, there was right ventricular strain (sometimes secondary to left heart failure) which could be the cause of pulmonary alternans. This could not be proved by others.[2]

2. *Impaired right ventricular contractility:* Five of the eight patients with pulmonary alternans had clinical right heart failure. This could have been secondary to left heart failure with right ventricular strain, or produced by direct ischemic involvement of the right ventricle. All of our patients with autopsy studies had some degree of right ventricular damage. The imbalance between oxygen supply and demand has already been proposed as one cause of mechanical alternans in aortic stenosis.[3] In some of our patients, the pulmonary alternans disappeared after the administration of strong inotropic drugs such as dopamine or digoxin, without significant changes in pulmonary pressure, cardiac index or pulmonary resistance levels, but perhaps with improvement in right ventricular contractility. We believe that even in cases without clinical evidence of right heart failure pulmonary alternans may indicate decreased right ventricular contractility.

All these findings are in accord with those observed by others[1,2,5,18] and prove that pulmonary alternans is a complex phenomenon that can be modified by more than one factor, and may depend on hemodynamic as well as on direct inotropic conditions.[2,4,19,26]

Prognostic significance: Pulmonary pulsus alternans in acute myocardial infarction is associated with a very high mortality rate. Half of the patients died while in the coronary care unit. The mortality rate was higher than in control patients in the same hemodynamic classification but without pulmonary alternans ($2P < 0.05$).

Mechanical alternans has previously been associated with a poor prognosis,[27,28] but other authors[2,5] believe that the severity of the underlying disease is what really determines the prognosis. Heart failure was more severe in patients with than in patients without pulmonary alternans; it was also more severe in the four patients with pulmonary alternans who died than in those who survived—another indication that the prognosis depends on the degree of heart failure.

Acknowledgment

We gratefully acknowledge the assistance of Dr. J. Calderon Montero from the National School of Chest Diseases, Madrid, Spain in performing the statistical analyses.

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Type A Personality and Extent of Coronary Atherosclerosis

JOEL E. DIMSDALE, MD*
THOMAS P. HACKETT, MD*
ADOLPH M. HUTTER, Jr., MD, FACC†
PETER C. BLOCK, MD, FACC†
DONNA CATANZANO, BS*

Boston, Massachusetts

The relation between type A personality and the extent of coronary artery disease was studied in 109 patients who underwent selective coronary angiography. Type A personality as measured with the Jenkins Activity Survey was not correlated with the extent of coronary artery disease as assessed from the number of vessels with 50 percent or greater narrowing of diameter.

In the past 15 years, there has been considerable research on the relation between the type A personality pattern and the occurrence of coronary events. Most noteworthy is the Western Collaborative Group Study,[1] a carefully designed investigation that followed up 3,500 men for 8 1/2 years. This study concluded that men characterized as manifesting type A behavior (hard-driving, intense competitive behavior) are at greater risk of having coronary heart disease than are men without such behavior (this group is called type B).

Recently, the type A pattern has been reported to be associated with increased coronary artery disease as demonstrated at cardiac catheterization.[2–4] Zyzanski et al.[2] found that men with type A behavior as measured with the Jenkins Activity Survey[5] had more coronary arteries with more than 50 percent narrowing than did men with type B behavior. Frank et al.[4] found a positive association between similarly defined coronary vessel disease and type A behavior as measured with an interview. Blumenthal et al.[3] found a positive association between the extent of coronary artery disease and type A behavior as measured with an interview but not as measured with the Jenkins Activity Survey. These studies have been regarded as provisional demonstrations of a pathophysiologic link between type A personality and the occurrence of heart disease. However, the discrepant results regarding the use of the Jenkins Activity Survey to predict coronary artery disease deserve further consideration. Zyzanski et al.[2] found a positive association; Blumenthal et al.[3] did not. Because the study of Blumenthal et al. included a large subset of women, their Survey scores are regarded as having questionable validity. The Jenkins Activity Survey itself has recently been criticized[6] as accurately classifying only 63 percent of type A and type B subjects. Other studies[7] reported that it accurately classifies 73 percent of subjects. Nevertheless, it is the most widely used objective scale for assessing type A personality.[8]

This study to test the hypothesis that type A personality is associated with an increased extent of coronary artery disease is intended to replicate the study of Zyzanski et al.,[2] not only in design, but also in characteristics of the population studied. Both studies examine Boston-based populations treated at two university hospitals, Massachusetts General Hospital and Boston University Medical Center.

From the Departments of Psychiatry* and of Medicine,† Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts.
This research was supported by Grant HL-19567 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.
Manuscript received November 28, 1977; revised manuscript received April 11, 1978, accepted May 3, 1978.
Address for reprints: Joel E. Dimsdale, MD, Massachusetts General Hospital, Boston, Massachusetts 02114.

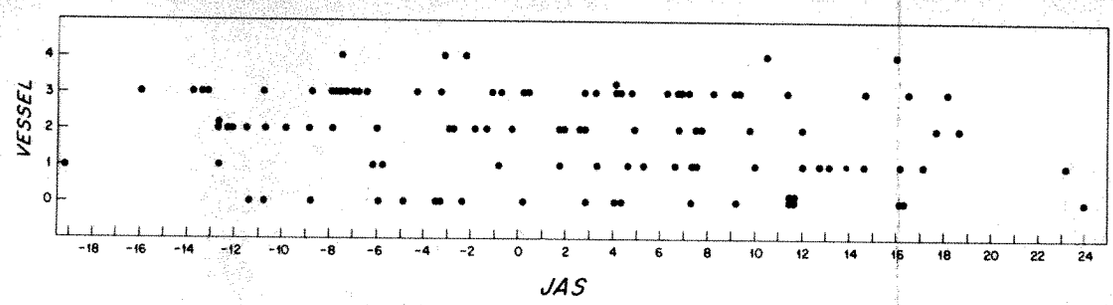


FIGURE 1. Relation between the number of diseased coronary vessels and Jenkins Activity Survey (JAS) score in 109 subjects. The positive Survey scores indicate type A personality, the negative scores type B personality.

Methodology

The study patients were selected from those awaiting cardiac catheterization at Massachusetts General Hospital. Indications for angiography were variable, but all patients had clinical evidence of coronary artery disease or worrisome chest pain of uncertain cause not elucidated by noninvasive testing. Patients were eligible for inclusion in the study if they (1) were 18 to 70 years old; (2) had apparent average intelligence; (3) were English-speaking; (4) had permission of their cardiologist; and (5) gave consent for study and were willing to cooperate in follow-up studies.

Patients were excluded from the study if they had evidence of valvular heart disease, a critical medical condition (such as cardiogenic shock) that might preclude adequate testing with the Jenkins Activity Survey or the presence of other major disease that might influence the 1 year follow-up (for example, malignancy). All such exclusions were made before personality assessment.

During a 1 year period, an attempt was made to contact 118 patients. The physician of three patients refused their participation; three patients were ineligible, and three refused participation. Thus, 109 patients, approximately 90 percent, were judged eligible and completed the evaluation. The sample included 99 men and 10 women. The average age was 49 years with a standard deviation of 9 years; 65 percent had a history of myocardial infarction and 55 percent had exertional angina (functional classes II, III and IV of the New York Heart Association).[9]

Patients were seen before cardiac catheterization and completed a Jenkins Activity Survey Form B as part of a larger risk factor inventory. This survey is an objective self-administered questionnaire designed to replicate closely the type A and B assignments that would be made in a Rosenman type A semi-structured interview.[5]

TABLE I

Average Jenkins Activity Survey (JAS) Scores* in 99 Men

Vessels Diseased (no.)	Patients (no.)	Mean JAS Score	Average Age (yr)	Age-Adjusted Mean JAS Score
0	16	2.99	44	2.85
1	18	6.38	48	6.53
2	25	−0.74	48	−0.86
3	35	1.01	51	1.48
4	5	2.74	54	4.21

* Positive Jenkins Activity Survey scores indicate type A personality, negative scores type B.

Cardiac catheterization was performed by a cardiologist who did not know the patients' Survey score. Coronary angiography was performed with the Sones or the Judkins technique. Angiograms were read by the cardiac radiologist, who also did not know the Survey score. A coronary vessel was considered significantly narrowed if angiography revealed 50 percent or greater narrowing of the vessel's diameter (equivalent to 75 percent cross-sectional narrowing of the vessel).

The relation between the number of vessels diseased and Jenkins Activity Survey score was plotted. A correlation analysis was performed. Because the score for vessels diseased ranged from 0 to 4, it is conceivable that the correlation techniques might be inappropriate. For this reason, the data were also reexamined with a t test contrasting the Jenkins Activity Survey scores of those with normal vessels or one vessel disease versus those with multiple vessel disease.

Results

The relation between the number of diseased coronary vessels and the Jenkins Activity Survey score for the total study population is shown in Figure 1. The regression line is negative with a slope of −0.02. The correlation coefficient itself is −0.12 and is not significant ($P < 0.20$). In view of the questionable validity of the Survey in women, we analyzed the male subsample alone. Table I presents for the 99 men the mean Jenkins Activity Survey score in each category of vessel disease. There was no trend toward increased Survey scores among patients with an increased number of diseased vessels. The severity of coronary disease was age-related in the sample ($r = 0.29$, $P < 0.01$); however, Jenkins Activity Survey scores were not significantly correlated with age ($r = -0.10$, $P > 0.1$). The Jenkins Activity Survey scores in each category of vessel disease were age-adjusted by the direct method[10] (Table I). Even after age adjustment, there is no clear trend relating type A personality as assessed with the Jenkins Activity Survey and extent of coronary artery disease.

A t test analysis was performed in two ways (Table II). In the first, comparing patients with no coronary vessel disease and patients with some significant vessel disease, the difference in Jenkins Activity Survey scores was not significant. In a second t test, comparing patients with no disease or single vessel disease with patients who had disease of more than one vessel, the Jenkins Activity Survey scores were significantly different ($P < 0.027$); however, the patients with *mild* disease had the higher Jenkins Activity Survey score

TABLE II

Jenkins Activity Survey Score and the Extent of Coronary Artery Disease in 99 Men

Coronary Artery Disease	JAS Score*	*t*	*P*
No	2.99		
versus		−0.49	>0.60
Some	1.75		
0 and 1 vessel	4.79		
versus		−2.24	<0.027
2 or more vessels	0.47		

* Positive scores indicate type A personality.
P = probability; *t* = *t* test value.

indicative of a type A pattern. These analyses were based on men alone, but the results were essentially unchanged by separate analyses including the 10 women from the sample. It is striking that in all of these statistical examinations, there was no evidence for a positive significant association nor even a trend toward a positive association between type A behavior and number of diseased vessels.

Discussion

Differences from previous studies: We were unable to confirm the findings of Zyzanski et al.,[2] who found a positive association between the extent of coronary artery disease and type A personality as measured with the Jenkins Activity Survey score. This major difference in findings is troublesome to interpret. Both studies were performed on a similar population—Boston-based patients who were seeking angiography at a teaching hospital. Both studies included only those for whom the Jenkins Activity Survey was standardized—basically a white male population. Both studies examined subjects with a similar age distribution and educational background. Both studies found a similar distribution of coronary artery disease.[11]

It is possible that the indications for cardiac catheterization may have been different for the two studies. In the study of Zyzanski et al. the group with no vessel disease included some patients with congenital valve disease. We considered such patients ineligible for our study. One might hypothesize that patients with congenital valve disease may have been required to lead slower less active lives and thus be more likely to manifest type B behavior. By comparison, a population with only coronary artery disease may represent the full continuum of type A and B personality patterns. If the patients with coronary artery disease are compared with the group with no vessel disease (which contains the group with valve disease) the former would appear to contain more persons with a type A personality. This difference in inclusion criteria may account for the difference in our results.

It is possible that unknown differences in the sample population affect the relation between type A personality and coronary artery disease. Researchers in this field have not yet elucidated the precise population

TABLE III

Jenkins Activity Survey (JAS) Score and Coronary Artery Disease in Four Clinical Subgroups of the 109 Patients

	Vessels Diseased (no.)	Mean JAS Score*	Patients (no.)
History of MI			
No	0	4.54	16
	1	0.4855	7
	2	0.54	8
	3	−0.12	6
	4	−7.50	1
Yes	0	1.540	5
	1	8.269	13
	2	−1.347	17
	3	0.066	32
	4	5.300	4
Severity of angina†			
Grades I and II	0	3.13	19
	1	5.63	16
	2	−0.6896	19
	3	1.081	21
	4	3.567	3
Grades III and IV	0	10.450	2
	1	5.199	4
	2	−0.9165	6
	3	−1.253	17
	4	1.500	2

* A positive score indicated type A personality, a negative score type B personality.
† New York Heart Association functional classification.
MI = myocardial infarction.

characteristics that are required to demonstrate an association between type A behavior and coronary artery disease. Ethnicity may seriously affect the determination of type A behavior.[12] The Boston University sample and the Massachusetts General Hospital sample may have differed in ethnic background sufficiently to affect the Jenkins Activity Score classification. The patient's experience with clinically significant disease may also affect the relation between type A behavior and coronary vessel disease; nevertheless, when our sample was subdivided according to extent of angina and history of past myocardial infarction, there was still no trend for a relation between type A personality and coronary vessel disease in any of the subgroups (Table III).

It is conceivable that type A determination, whether with the Jenkins Activity Survey or an interview, is made difficult by anxiety-arousing circumstances such as hospitalization. However, this problem is common to all the other studies of this type.[2–4] It seems unlikely that our patients were somehow more anxious than those undergoing angiography in the other studies. Although it is not clear which factors may account for the different findings, one must consider that the evidence favoring an uncomplicated association between type A personality as assessed with the Jenkins Activity Survey and the extent of coronary artery disease is unconfirmed and under some question.

Implications: From this study no inference can be made regarding the ability of the type A *interview* as

sessment to predict the extent of coronary artery disease. Because the Jenkins Activity Survey has recently come under some criticism,[6] it would be important to perform a similar study utilizing the same methodology but measuring type A behavior with the type A structured interview. This work is in progress and will be reported on in a future publication.

The data in all the studies relating coronary angiographic findings to personality type are retrospective and thus cannot exclude the possibility that symptomatic heart disease may have modified the type A behavior by the time the patient arrived for cardiac catheterization. Finally, type A behavior may be interacting with the heart on other pathophysiologic levels, such as plasma catecholamines or lipids. From the present study one must conclude that type A behavior, as measured with the Jenkins Activity Survey, is not positively associated with the extent of coronary artery disease found on cardiac catheterization.

Acknowledgment

We thank Steve Zyzanski, PhD for processing the Jenkins Activity Survey questionnaires and John Gilbert, PhD for statistical consultation.

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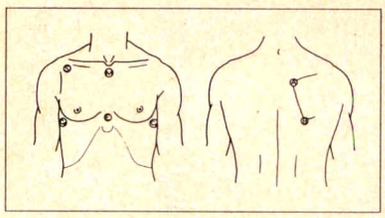
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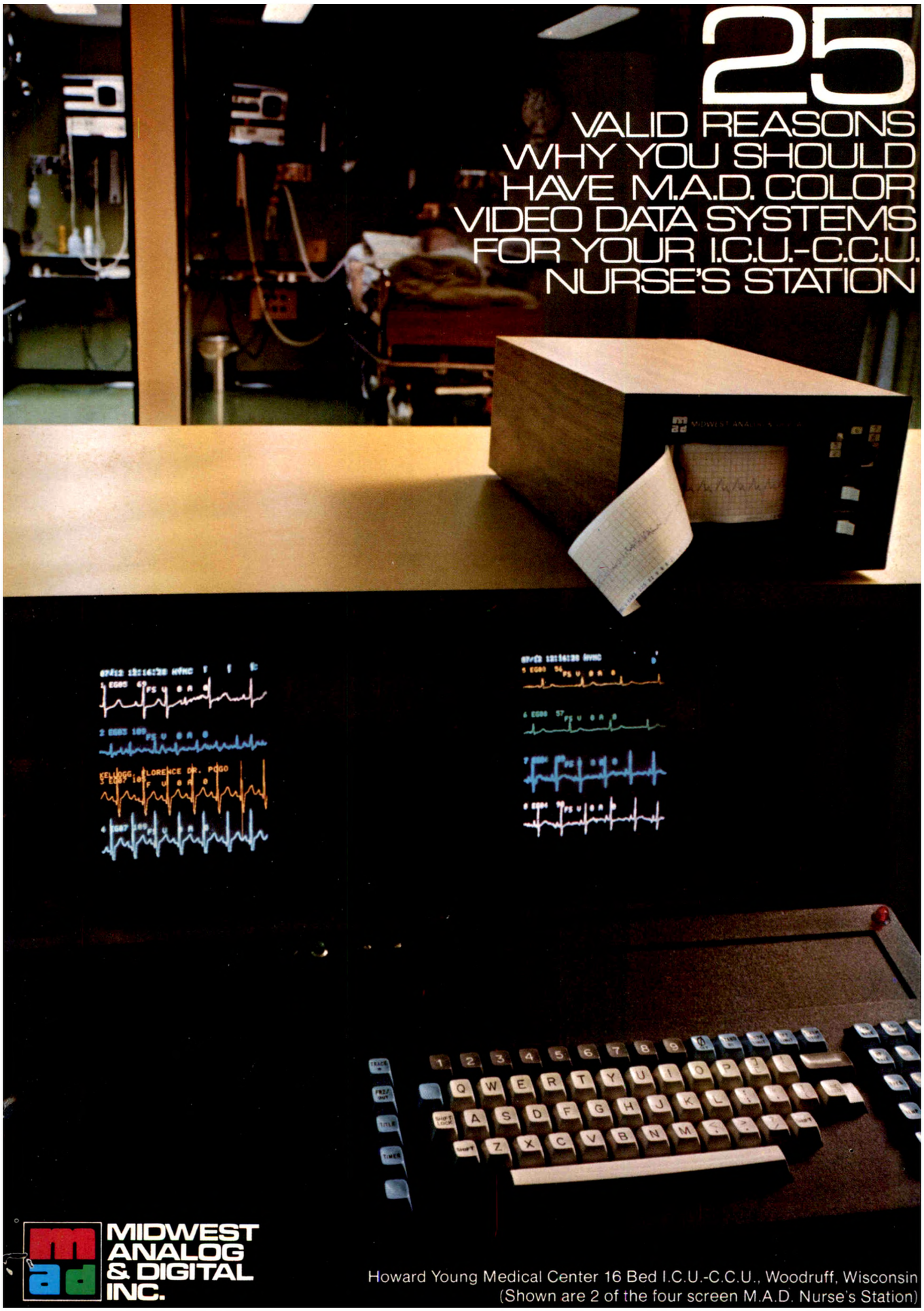
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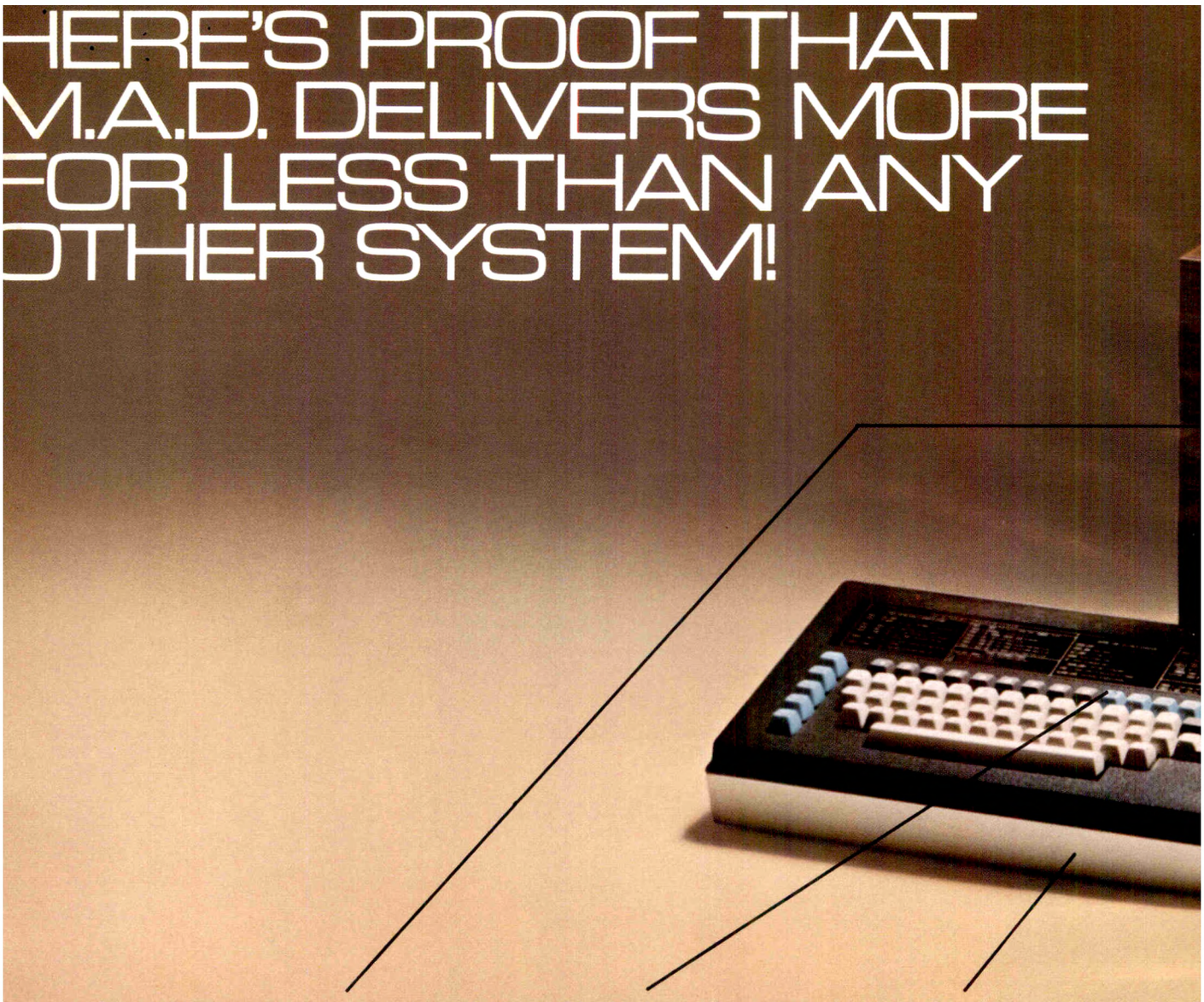
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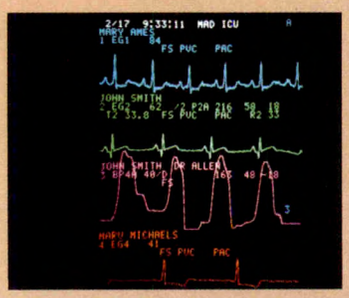
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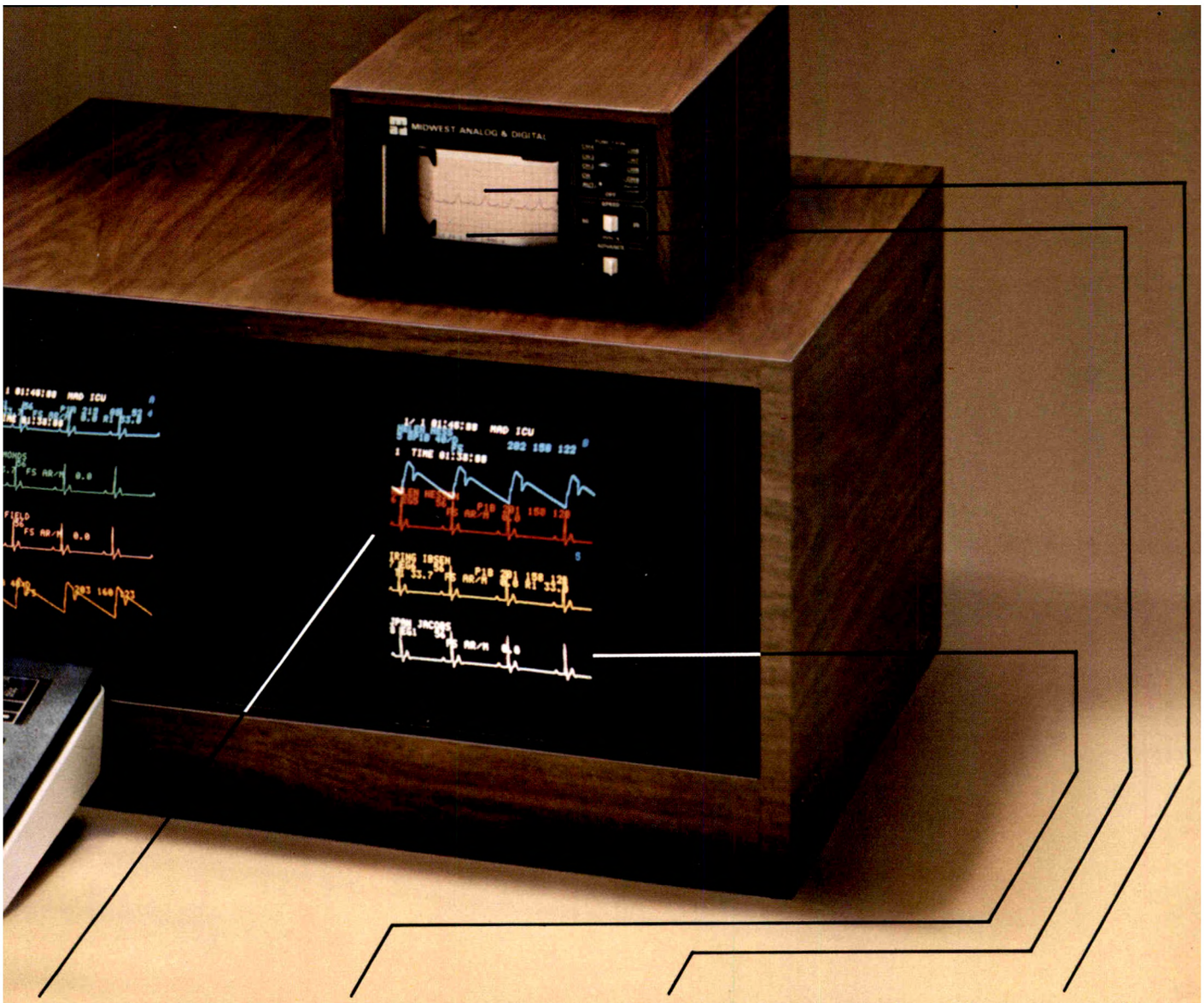
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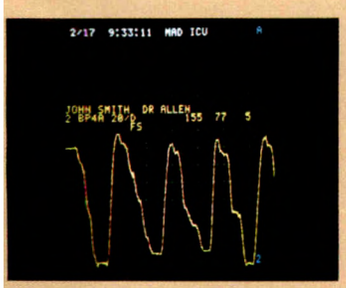


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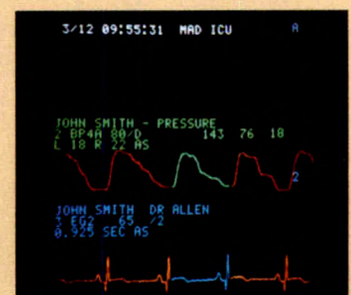
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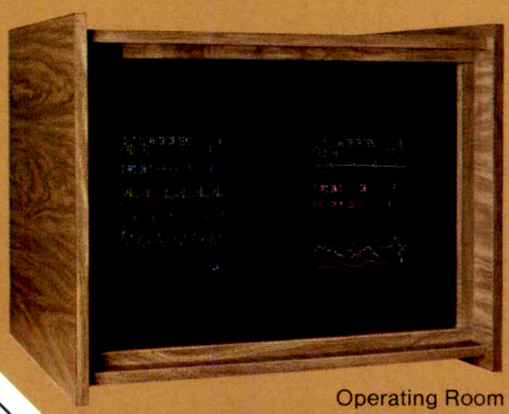
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Decreases blood pressure with less potential for bronchospasm

Lopressor, a relatively selective beta blocker, is an effective and well-tolerated antihypertensive.

Lopressor exerts a preferential effect on the beta receptors involved in lowering blood pressure and has less effect on beta receptors not involved in blood pressure control.

It concentrates its action on beta receptors in the heart (β_1) and leaves beta receptors in the lungs (β_2) relatively unblocked.

WARNING: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. However, Lopressor may be prescribed with caution for hypertensives with asthma or COPD who do not respond to, or cannot tolerate, other antihypertensive therapy. Since β_1 selectivity is not absolute and diminishes with increased dosage, a β_2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval.

Logical complement to a diuretic

The effectiveness of Lopressor combined with a diuretic was demonstrated in a study* of 15 hypertensive patients whose blood pressure was reduced on a thiazide alone, and still further reduced when metoprolol was added to the regimen. On a regimen of 100 mg hydrochlorothiazide daily, the maximal response was a mean supine blood pressure reduction of 19/10 mmHg —from a placebo-treatment baseline level of 169/115 mmHg. Following four weeks during which metoprolol 50 mg b.i.d. was added to the regimen, there was a further decrease of 17/13 mmHg.

Mild, transient side effects

Most side effects are mild and transient. The most frequently reported adverse reactions (which

*Mitenko P, McKenzie J: Unpublished study. Data on file, Geigy Pharmaceuticals and available on request.

Usually lacks the side-effect problems of the sympathetic inhibitors

occurred in approximately ten out of 100 patients) are tiredness and dizziness. Depression and diarrhea have occurred in about five out of 100.

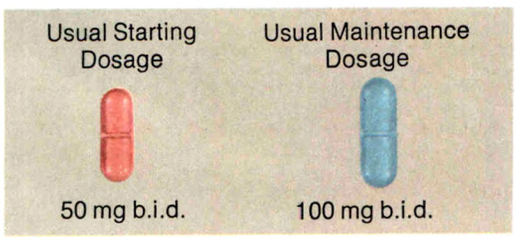
Lopressor usually lacks the side effects of the sympathetic inhibitors which may cause sedation, sexual dysfunction and postural hypotension.

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

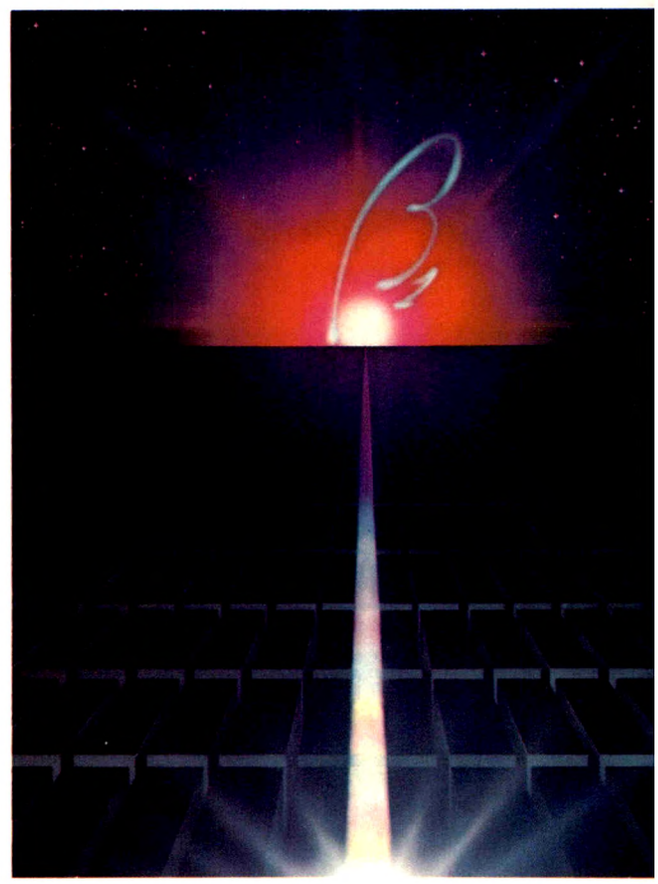
There have been reports of exacerbations of angina pectoris and, in some cases, myocardial infarction following *abrupt* cessation with other beta blockers. Even in the absence of overt angina pectoris, when discontinuing therapy, withdraw Lopressor slowly.

Simple b.i.d. dosage

Patient adherence to the regimen is likely with Lopressor because of its easy-to-remember b.i.d. dosage schedule. The usual starting dosage is one 50-mg tablet twice a day. The usual maintenance dosage is one 100-mg tablet twice a day.



While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control *is* being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. For further details, please see brief summary of prescribing information.



Extensive experience worldwide

Over 240,000 patients have been treated with metoprolol in 21 different countries.

Please see last page for brief summary of prescribing information.

The relatively selective beta blocker for hypertension–with simple b.i.d. dosage

Geigy

Lopressor™
brand of metoprolol tartrate

An antihypertensive beta-blocking agent

Indications Lopressor, brand of metoprolol tartrate, is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor, brand of metoprolol tartrate, is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor, brand of metoprolol tartrate, should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor, brand of metoprolol tartrate, therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor, brand of metoprolol tartrate, should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor, brand of metoprolol tartrate, may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor, brand of metoprolol tartrate, should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor, brand of metoprolol tartrate, plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor, brand of metoprolol tartrate, should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, Raynaud's disease, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor, brand of metoprolol tartrate, during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor, brand of metoprolol tartrate, should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor, brand of metoprolol tartrate, is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

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The name Quinton has long been the hallmark in the design and manufacture of treadmills for use in controlled exercise. Now, with the Model 633 three channel stress test monitor, Quinton offers a total system to make controlled stress testing accurate, repeatable and economical.

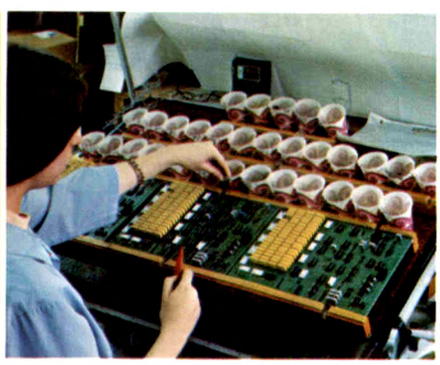
The Quinton system makes it possible for a stress testing laboratory, clinic or hospital to initiate a sophisticated test program with a moderate investment.

The Quinton system includes a time-tested Quinton Treadmill. There is a model available for virtually every application — all featuring the Quinton-pioneered endless nylon belt and "no-jerk" speed control. The treadmill is teamed with the Model 633 stress test monitor, with its advanced standard features and "plug-in" options. Together, they create the unbeatable system!

FEATURES OF THE MODEL 633

- Three channel non-fade scope with write-from-memory capability
- Three channel ECG recorder with continuous output for signal analysis
- Automatic 12-lead rotation for testing ECGs
- Low noise, shielded patient cable for optimum results during exercise
- Scope displayed digital heart rate meter
- Plus a sturdy, attractive control console which provides room to expand test capabilities with easy "plug-in" optional features such as ECG data computer... S-T computer... defibrillator...and automatic exercise control programmer which regulates both slope and speed automatically to meet your protocol needs.






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YOU CAN'T BEAT THE SYSTEM

78-2

Sir Isaac Newton's gift was the rare ability to question, to envision, and to apply...

That same special ability has brought Intermedics to the forefront of pacemaker technology.



Introducing the CyberLith.™ A landmark innovation from Intermedics.

Sir Isaac Newton's introduction of the concept of gravity immensely enriched man's understanding—and control—of his world. Similarly, the CyberLith pulse generator gives you, the physician, unprecedented control of pacemaker therapy for the individual patient. With the CyberLith, pacemaker functions can be adjusted *precisely* and titrated to an exact prescription for each patient.

The CyberLith offers:

- *15 pacing rates*
- *15 pulse widths*
- *7 sensitivity levels*
- *3 operating modes plus advanced telemetric circuitry for detailed, non-invasive performance monitoring.*

Maximum responsiveness to varying patient needs with fifteen pacing rates.

The CyberLith pulse generator can be programmed to a pacing rate appropriate to virtually any pacemaker patient case. Your patients are individuals with individual pulse rate requirements that can and do change with time. The CyberLith pacemaker's fifteen rates, from 30 to 120 bpm, offer you maximum versatility in meeting individual patient needs.

Vital flexibility with a range of fifteen pulse widths.

A choice of pulse widths from 0.15 to 2.29 msec assures effective pacing for each patient. Variations in optimal pulse width may occur as a result of the change from acute to chronic stimulation threshold levels. Other variations may be due to myocardial fibrosis, drug therapy regimens, or electrode type and position. With the CyberLith, battery longevity can be maximized through selection of the shortest pulse width needed to ensure adequate capture.

"Fine-tuning" control with a choice of seven sensitivity levels.

The CyberLith makes possible precise sensitivity adjustments in response to different clinical situations. For example, if T-waves or other artifacts are being sensed to the detriment of proper system functioning, the CyberLith pacemaker's sensitivity can be reduced to a more desirable level. Conversely, inadequate or inconsistent sensing of the QRS complex may be corrected by increasing the programmed sensitivity.

Unique versatility: three pacing modes.

The CyberLith may be programmed to the mode best suited to your patient's condition and environment. You may choose among three pacing modes:

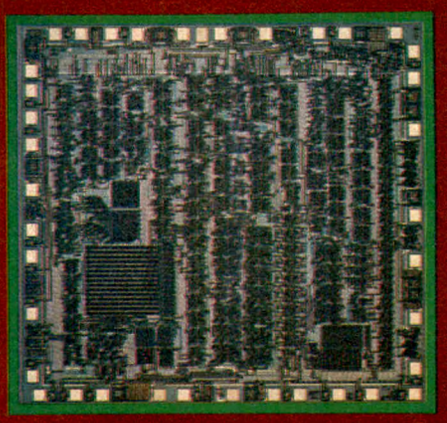
—R-wave inhibited (demand)
—asynchronous (fixed-rate)
—R-wave synchronous (demand)

Thus the CyberLith may be reprogrammed in response to indications for a different pacing mode, without the need for surgical intervention.

Telemetric communication with the implanted pacemaker system.

The CyberLith pacemaker's exclusive telemetry feature permits you to ascertain the precise status of the implanted





Intermedics' custom complementary metal-oxide semiconductor integrated circuit magnified approximately 11 times.

Actual size of c-mos "chip" as it is employed in the CyberLith.

system to a degree never before possible.

—battery voltage
—battery impedance
—electrode lead impedance
—exact timing of sensing *and* pacing events

can all be determined simply, for detailed evaluation of pacer operations. In addition, CyberLith telemetry makes possible more accurate estimation of the remaining service life of the unit.

Big features in a small package, through microminiaturized circuitry.

The CyberLith packs a multiplicity of programming features into a remarkably small pulse generator. One reason this can be achieved is the use of a custom complementary metal-oxide-semi-conductor (c-mos) integrated circuit. This "chip" has been specially developed by Intermedics for use in the CyberLith and represents state-of-the-art semiconductor technology. The c-mos circuitry reduces the total number of components and simplifies the design of the CyberLith. The result is an unprecedented range of programmable pacing parameters with remarkably low power consumption.

Fail-safe programming at your fingertips.

Advanced design concepts have been incorporated into the programming system to ensure *safe, trouble-free operation.*

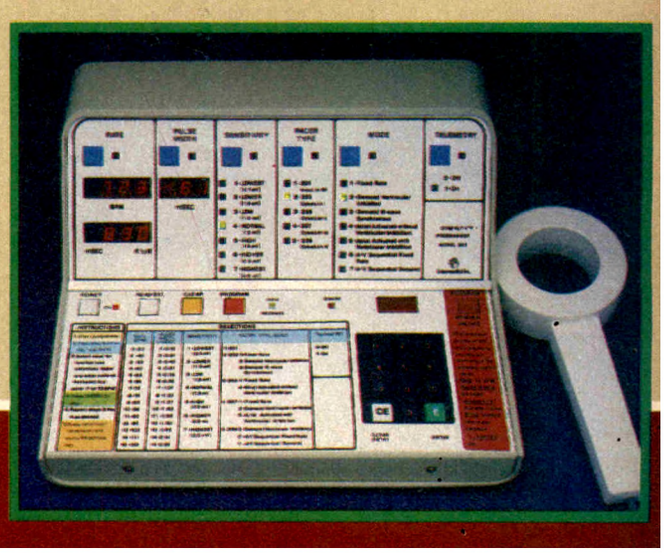
—The programmer is portable and uses rechargeable batteries to prevent unwanted electrical noise and other complications common to line-powered instruments.
—Programmable features may be altered individually or simultaneously.
—Accidental reprogramming is virtually impossible, thanks to the precise state-of-the-art crystal oscillator technology in combination with pulse-position-modulated, binary coded data security.
—A unique feature permits immediate reprogramming to *original nominal pacer parameters* by depressing a single button on the programmer panel.

These characteristics make the CyberLith programming system easy to use, and provide an added margin of safety for you and your patient.

The CyberLith—it's making history. Now.

Your Intermedics representative can provide you with additional information on the many other advantages of CyberLith therapeutic pacing, such as amazingly compact size, redundant oscillator circuitry and *positive confirmation of reprogramming.*

At Intermedics, we are producing tomorrow's technology today, because OUR BUSINESS IS LIFE.





Free limited-edition print offer from Intermedics, Inc.

The Newton watercolor, by artist Ron Adair, is first in a series commissioned by Intermedics. The original work hangs in Intermedics' corporate headquarters. A limited-edition print, numbered and signed by the artist and suitable for framing, is being made available by Intermedics to physicians only. Please write to Marketing Administration, Intermedics, Inc., P.O. Box 617, Freeport, Texas 77541.

Note: The CyberLith is currently undergoing clinical evaluation and is not routinely available on a commercial basis.

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CyberLith is a trademark of Intermedics, Inc., Freeport, Texas.

Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and relatively widely variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Microwave ovens that do not exceed federal guidelines for leakage (0.5 mW/cm^2 at 2.5 cm from the appliance) will not affect the pacemaker, but leakage in excess of that amount may cause interference. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

Intermedics Inc.
P.O. Box 617 Freeport, Texas 77541
Tel: (713) 233-8611

Our business is life.

4 critical criteria in choosing a Holter service

Before you select a Holter service, make sure it meets these 4 important standards. Telemed does!

1. Technician Specialization.

Scanning a long term ECG tape is a specialty requiring intense concentration.

Telemed makes sure this concentration is not disturbed. Holter monitoring is the only responsibility our Holter technicians have. This not only sharpens their focus, but also better enables them to spot meaningful events, morphologic changes, arrhythmias, even slight abnormalities.

2. Non-Fatiguing Technician Workload.

Volume is important to any Holter scanning service, but Telemed never puts quantity ahead of quality. Telemed's "Always Alert" Policy limits the number of tapes a Holter technician can scan per day. This minimizes fatigue, so technicians are more alert, ready to recognize changes no matter how slight.

3. Emergency Alert.

Telemed provides a double assurance that you are notified immediately if any life threatening abnormalities appear. Double assurance because both the Holter technician and a staff cardiologist review each scan for events which require your immediate attention. You are notified at once when such events are spotted.

4. Continuous Dual-Channel Equipment.

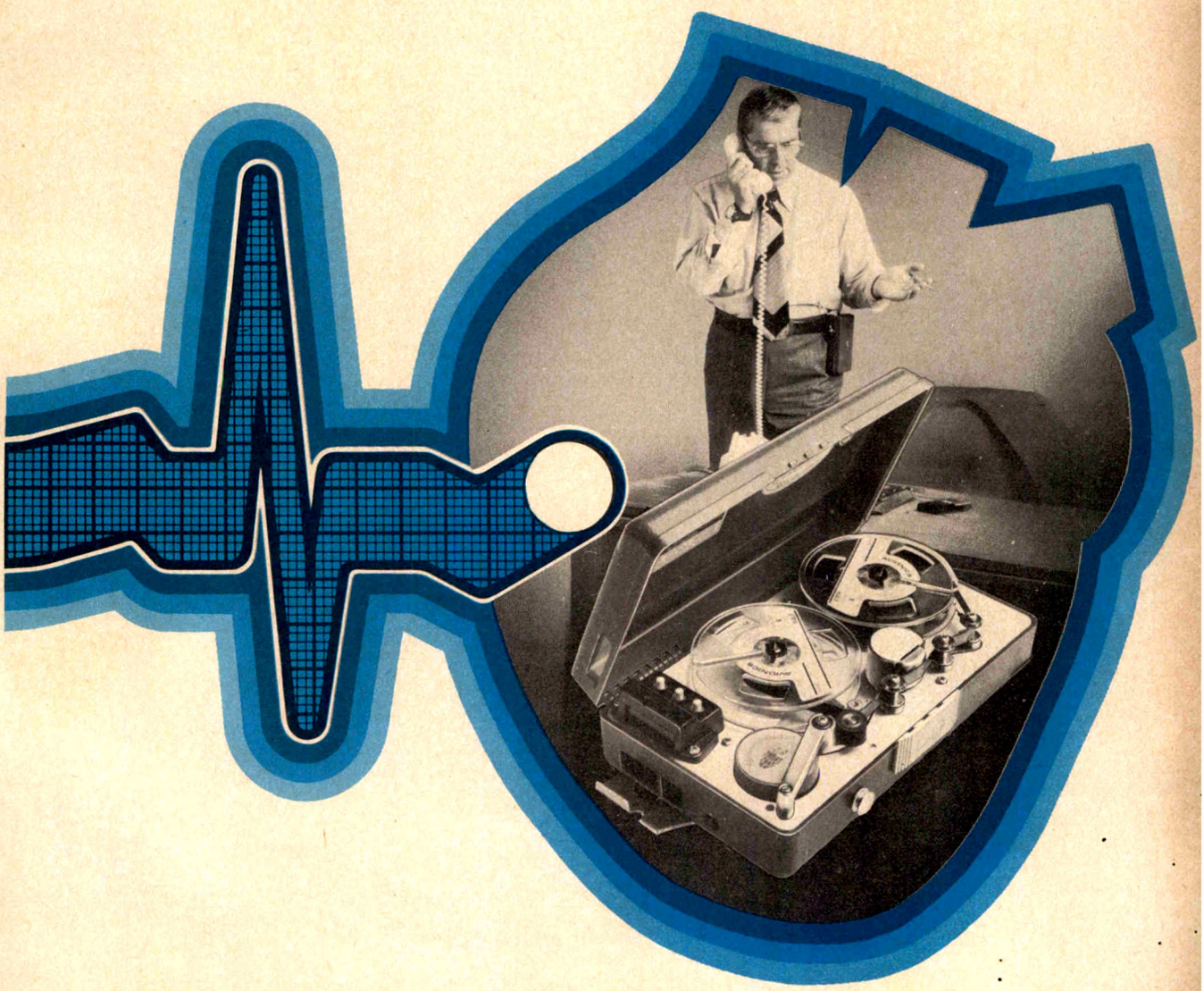
The Telemed Holter Scanning Service features state-of-the-art, continuous dual-channel monitoring equipment for greater reliability in arrhythmia detection and in the diagnosis of coronary artery disease.

Telemed's Holter Scanning Service includes tapes, patient diaries, mailers, service and maintenance. Plus Telemed trains your personnel at no extra charge. For full details on how Telemed Holter Scanning can help you help your patients, call or write Telemed today.

Telemed's Holter Scanning Service meets all four crucial standards.

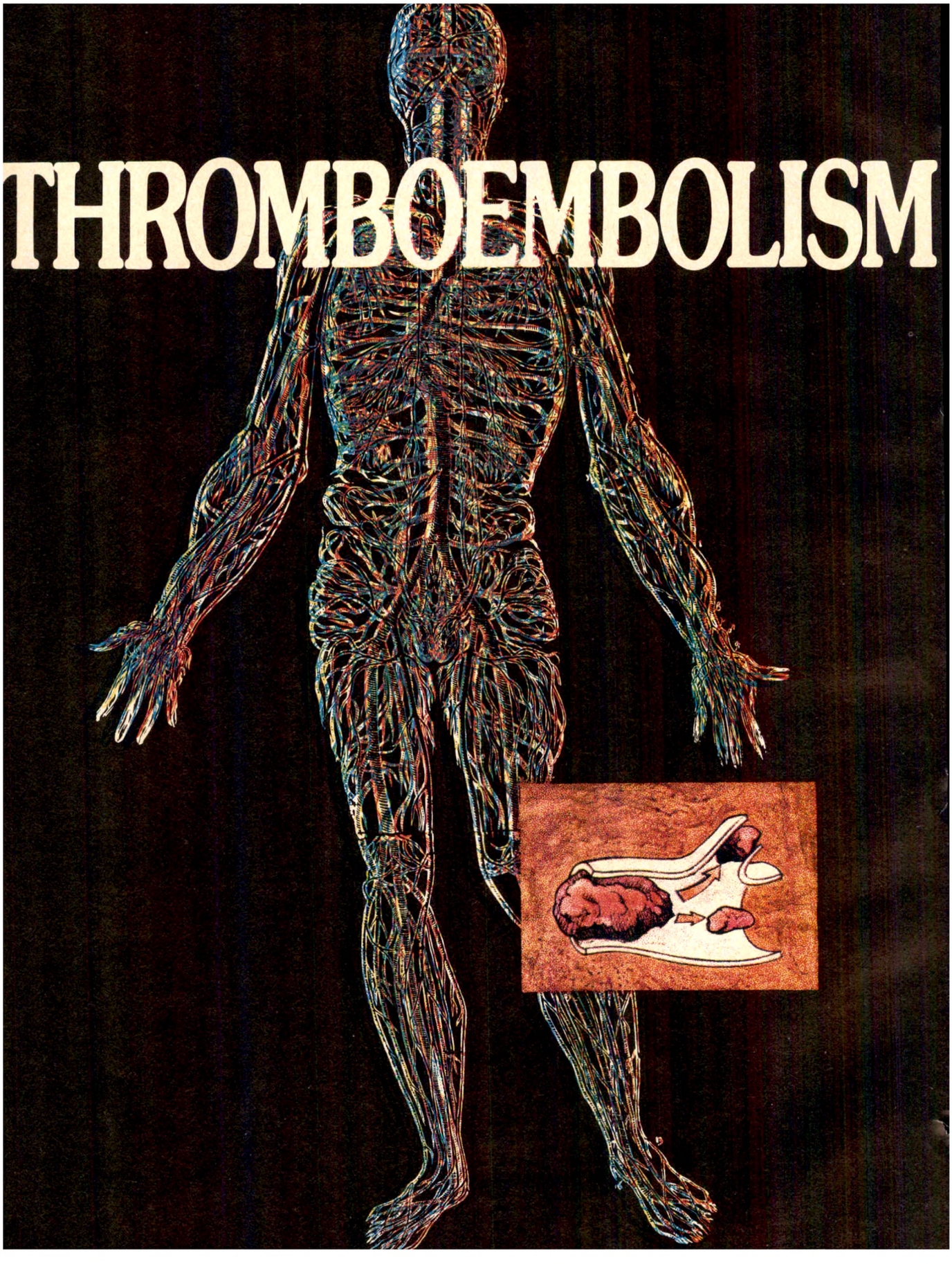
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CORPORATION

2345 Pembroke Avenue
Hoffman Estates, IL 60195
312/884-5900



A65

THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy–COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus; and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN* with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN* may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN*, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN* may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

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Printed in U.S.A.

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EDO-046C

March, 1977

Effect of Lidocaine on Conduction in the Ischemic His-Purkinje System of Dogs

GARY GERSTENBLITH, MD*
BENJAMIN J. SCHERLAG, PhD, FACC†
RONALD R. HOPE, MD†
RALPH LAZZARA, MD, FACC†

Miami, Florida

The effect of lidocaine on His-Purkinje conduction in dogs with ischemic damage to the His bundle was compared with the effect of lidocaine in normal dogs. The anterior septal artery was ligated in 14 dogs, and 30 minutes later atrial pacing was performed to increase residual ischemic damage. Four to 6 days later, His bundle recordings were obtained during sinus rhythm and atrial pacing before and after the administration of lidocaine in a dose of 2 mg/kg and a total dose of 4 mg/kg. His bundle recordings were also obtained in nine control animals before and after the administration of lidocaine. Lidocaine significantly increased the H-V time in the animals with ischemic damage during sinus rhythm and at all pacing rates. It also resulted in advanced His-Purkinje conduction defects including His bundle block and right bundle branch block in these animals. In contrast, the effect of lidocaine in the normal animals was negligible. It is concluded that lidocaine significantly depresses His-Purkinje conduction in the setting of preexisting ischemic damage. These results suggest that lidocaine may be used as a diagnostic tool to unmask latent His-Purkinje conduction defects due to ischemia.

The effect of lidocaine on His-Purkinje conduction in normal hearts is reported to be slight[1,2]; its effect on conduction in the presence of preexisting ischemic damage to the His-Purkinje system has not been thoroughly evaluated. A reasonable hypothesis is that its action would differ in these circumstances because microelectrode studies have demonstrated that lidocaine's electrophysiologic action in acutely ischemic Purkinje cells differs considerably from its action in normal cells.[3] In addition, electrograms recorded in open chest dog preparations have shown that, although lidocaine has no effect on normal cardiac muscle, it delays activation, increases the effective refractory period and abolishes conduction in reentrant pathways in ischemic cardiac muscle.[4,5] In this study, ischemic damage to the His bundle and the proximal bundle branches was induced in dogs by ligation of the anterior septal artery. Four to 6 days later, the effect of lidocaine on His-Purkinje conduction during sinus rhythm and atrial pacing was determined.

Methods

Experimental procedure: Sixteen adult mongrel dogs weighing 12 to 18 kg were anesthetized with 30 mg/kg body weight of intravenous pentobarbital. The animals were intubated, placed on a respirator using room air and attached to an electrocardiograph for continuous monitoring. The left vagosympathetic trunk was isolated. Silver electrodes were inserted into the vagal trunk, and stimulation was accomplished using a Grass S88 stimulator that delivered 0.05 msec square wave pulses of 1 to 20 v intensity at a frequency of 20 hertz through a stimulus isolation unit. A thoracotomy was performed in the fourth left intercostal space and the heart exposed by pericardiotomy. The left atrial appendage was reflected, and the left coronary artery was dissected from the surrounding tissue at the bifurcation of the anterior descending and circumflex

From the Department of Cardiology, Veterans Administration Hospital and the University of Miami, Miami, Florida. This work was supported in part by Grant HL 18139 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received April 11, 1978; revised manuscript received June 6, 1978, accepted June 7, 1978.

† Present address: Cardiology Division, Veterans Administration Hospital, Oklahoma City, Oklahoma.

* Present address and address for reprints: Gary Gerstenblith, MD, 565 Carnegie Building, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, Maryland 21205.

branches. The anterior septal artery arises from the posterior surface of the left coronary artery either at the bifurcation or within 2 to 3 mm of it along the course of the anterior descending or, rarely, the circumflex artery.[6–8] The anterior septal artery was isolated in this region and occluded with a silk ligature. During the following 30 minutes, vagally induced slowing of the heart rate was used in an attempt to decrease the incidence and severity of ventricular arrhythmias. At the end of this time, pacing was performed with a bipolar plunge wire inserted into the atrial appendage or an electrode catheter passed through the external jugular vein into the right atrium and use of a Grass S88 stimulator with a stimulus isolation unit. Pacing was performed because preliminary experiments had indicated that resultant His-Purkinje damage was greater when the conduction system was stressed in this manner shortly after ligation. Pacing was continued for 60 to 90 minutes at a rate fast enough to elicit atrioventricular (A-V) nodal, His bundle or bundle branch block, which occurred at a rate of 240 to 300 beats/min. The chest was then closed.

Lidocaine protocol and His bundle recordings: Four to 6 days later the animals were again anesthetized and intubated. The left external jugular vein and carotid artery were isolated. An electrode catheter passed through the external jugular vein was used for atrial pacing, and another catheter was passed into this vein for the administration of lidocaine. A no. 5F catheter containing unipolar ring electrodes 1 cm apart was passed from the common carotid artery to the aortic root for recording His bundle activation.[9] In addition, His bundle recordings were obtained, when possible, through a catheter passed in retrograde manner from the femoral vein to the region of the tricuspid valve. All records, including electrocardiograms, were obtained on a multichannel Electronics for Medicine oscilloscopic photographic recorder at a paper speed of 25 to 200 mm/sec with a filter frequency of 0.1 to 200 hertz for electrocardiographic leads and 40 to 200 hertz for electrographic recordings. These recordings were obtained during sinus rhythm and atrial pacing at rates of 180, 210 and 240 beats/min. A bolus dose of 2 mg/kg of lidocaine was administered, and after 1 minute the recordings were repeated. A second bolus dose of 2 mg/kg of lidocaine was immediately administered, resulting in a total dose of 4 mg/kg, and the pacing experiment was repeated. When 1:1 A-V conduction failed at a constant pacing rate because of A-V nodal Wenckebach block or His bundle block, the H-V interval could not be measured. This occurred in several animals at heart rates of 270 and 300 beats/min and in the animals with ischemia at a heart rate of 240 beats/min after administration of the second dose of lidocaine. The effect of lidocaine was also examined in an identical manner in nine control dogs whose anterior septal artery was not ligated.

Analyses: At the end of the study the heart was excised. The extent of gross myocardial infarction of the basal interventricular septum and the anatomic distribution of the ligated anterior septal artery were examined. All animals showed visible evidence of necrosis at the base of interventricular septum subjacent to the His bundle and proximal right and left bundle branches.

The data were analyzed using the mean value of the H-V interval from three beats measured to the nearest millisecond at each heart rate during the control period and after each dose of lidocaine in each animal. The mean value and standard error for each group of animals under each condition was calculated, and the significance of any difference between the groups was assessed using Student's t test for paired values.

Results

Control animals: Electrocardiograms and His bundle recordings obtained during sinus rhythm in the control animals were all within normal limits. The mean H-V time was 28.5 ± 0.8 msec. The effect of lidocaine on the H-V interval during sinus rhythm and atrial pacing in the control animals is shown in Table I. During sinus rhythm and at pacing rates of up to 240 beats/min, administration of lidocaine resulted in a slight increase in the H-V interval, which was significant only if the control value at a pacing rate of 180 beats/min was compared with the value obtained after administration of the total dose of lidocaine (4 mg/kg) at the same pacing rate. No intra-His block, block distal to His or bundle branch block patterns in the electrocardiogram

TABLE I

Effect of Lidocaine on the H-V Interval (msec) in Normal Animals During Sinus Rhythm and Atrial Pacing

	Sinus Rhythm	Atrial Pacing (rate/min)		
		180	210	240
Control	28.5 ± 0.8 (9)	28.2 ± 1.1 (9)	28.4 ± 1.1 (9)	29.0 ± 1.3 (9)
Lidocaine				
2 mg/kg	+0.6 ± 0.9 (9)	+0.7 ± 0.9 (9)	+0.8 ± 0.8 (9)	+1.9 ± 0.8 (9)
4 mg/kg	+0.6 ± 1.1 (7)	+2.0 ± 0.7* (7)	+2.2 ± 1.0 (7)	+2.4 ± 1.8 (7)

* $P < 0.05$ compared with control value.
Numbers in parentheses refer to the number of animals.

TABLE II

Effect of Lidocaine on the H-V Interval (msec) in Ischemic Animals During Sinus Rhythm and Atrial Pacing

	Sinus Rhythm	Atrial Pacing (rate/min)		
		180	210	240
Control	35.4 ± 3.6 (11)	36.5 ± 3.8 (11)	36.7 ± 3.6 (11)	37.1 ± 3.9 (11)
Lidocaine				
2 mg/kg	+2.0 ± 0.9* (10)	+2.6 ± 1.0* (10)	+3.4 ± 0.9† (11)	+4.1 ± 1.2‡ (11)
4 mg/kg	+3.9 ± 1.4* (10)	+3.7 ± 1.5* (10)	+4.9 ± 1.4† (10)	

* $P < 0.05$, † $P < 0.01$ and ‡ $P < 0.005$ compared with control value.
Numbers in parentheses refer to the number of animals.

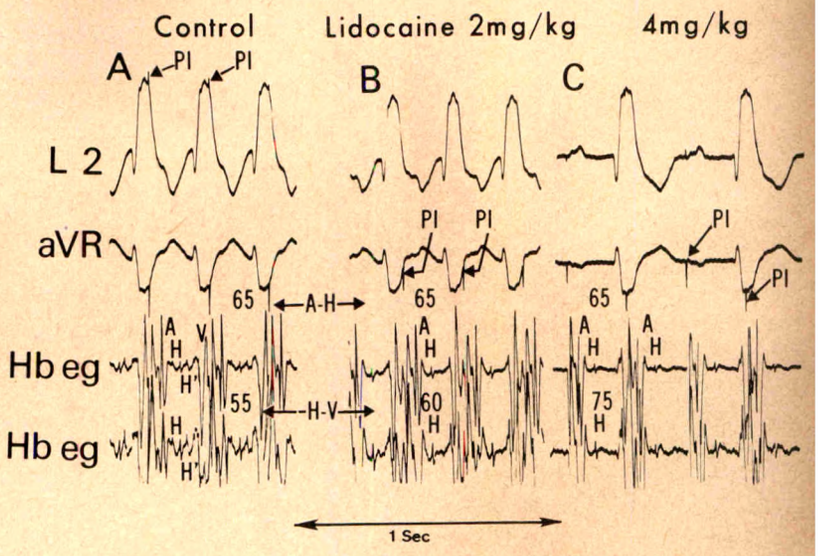


FIGURE 1. Electrocardiographic leads II (L2) and aVR and two simultaneously recorded His bundle electrograms (Hb eg) from a dog 4 days after ligation of the anterior septal artery. **A,** in the control tracing, atrial pacing at a rate of 270 beats/min was associated with a split His potential and an H-V time of 55 msec. **B,** after the administration of 2 mg/kg of lidocaine, the H-V interval increased to 60 msec. **C,** after the administration of a total dose of 4 mg/kg of lidocaine, 2:1 His bundle block developed. A = atrial deflection; A-H = time from atrial to His bundle deflection in msec; H = His bundle deflection; H-V = time from His to ventricular deflection in msec; PI = pacemaker impulse.

occurred in the control animals either before or after administration of lidocaine at any pacing rate.

Animals with ischemic His-Purkinje system: The effect of lidocaine on the H-V interval during sinus rhythm and atrial pacing in the animals with ischemia is shown in Table II. The H-V interval increased significantly during sinus rhythm and at all pacing rates at both concentrations of lidocaine. This increase was more pronounced at faster pacing rates and the greater lidocaine concentration. For example, after the administration of a 2 mg/kg dose of lidocaine, the mean H-V interval increased 2.0 ± 0.9 msec during sinus rhythm and 4.1 ± 1.2 msec at a pacing rate of 240 beats/min. At a pacing rate of 210 beats/min, the H-V interval increased an average of 3.4 ± 0.9 msec and 4.9 ± 1.4 msec after the first and second doses of lidocaine.

Several animals had more advanced conduction abnormalities at higher pacing rates. The findings in one of these animals is presented in Figure 1. During sinus rhythm at a paced rate of 270 beats/min, complete left bundle block was present. Atrial pacing resulted in an increase in the H-V interval from 41 to 55 msec and a split His potential. After the 2 mg/kg dose of lidocaine was administered, the H-V interval increased to 60 msec. After the total dose of 4 mg/kg was administered, 2:1 His bundle block, defined as block distal to the recorded His bundle potential, developed.

A summary of the His-Purkinje conduction abnormalities in the animals with ischemia is presented in Table III. A spectrum of conduction abnormalities was present. Three animals, group A, had advanced His-Purkinje conduction disturbances during sinus rhythm alone. Two had 2:1 His bundle block and one complete heart block. In these three animals the lidocaine pacing protocol could not be performed. In addition, in six

TABLE III

Advanced His-Purkinje Conduction Defects in Animals With Ischemia

Sinus Rhythm	Atrial Pacing	Atrial Pacing and Lidocaine (2 mg/kg)	Atrial Pacing and Lidocaine (4 mg/kg)
	Group A (3 animals)		
Complete heart block (1)	...	...	...
2:1 His bundle block (2)	...	...	...
	Group B (5 animals)		
LBBB	LBBB; split His potential (H-H′ = 17 msec)	His bundle block at 270/min	His bundle block at 270/min
None	None	RBBB at 300/min	RBBB at 240/min
None	His bundle block at 300/min	His bundle block at 270/min	His bundle block at 225/min
Split His potential (H-H′ = 26 msec)	Split His potential (H-H′ = 37 msec)	His bundle block at 300/min	His bundle block at 300/min
Split His potential (H-H′ = 11 msec)	Split His potential (H-H′ = 11 msec)	Split His potential (H-H′ = 18 msec)	Split His potential (H-H′ = 18 msec)
	Group C (6 animals)		
None	None	None	None

Numbers in parentheses refer to the number of animals. LBBB = left bundle branch block; RBBB = right bundle branch block.

animals, group C, no conduction abnormalities were present during sinus rhythm or atrial pacing either before or after administration of lidocaine. However, the five animals in group B had His-Purkinje conduction defects that were either induced or exacerbated by lidocaine. Thus, lidocaine caused His bundle block and right bundle branch block to occur in three of these animals that had not previously manifested these defects, caused His bundle block to occur at a slower pacing rate than previously in one animal and slowed intra-His conduction, resulting in a longer H-H′ conduction time, in one animal.

Thus, lidocaine significantly increased the mean H-V intervals in all animals studied. Lidocaine impaired His-Purkinje conduction sufficiently to induce or exacerbate His bundle block or right bundle branch block in 5 of 11 animals that had ischemic damage to the His-Purkinje area but in none of the 9 control animals that did not undergo ligation of the anterior septal artery ($P < 0.05$, Fisher-Yates exact test, one tail).[10]

Discussion

Effect of lidocaine on normal conduction system: The effect of lidocaine on His-Purkinje conduction in normal tissue has been reported to be minimal.[1,2] Sugimoto et al.[1] reported increases of 1.6 and 2.4 msec in the His to peripheral Purkinje conduction time in normal awake dogs after the administration of lidocaine in bolus doses of 2 mg/kg and 4 mg/kg, respectively. Lieberman et al.[2] reported no change in His to septal activation time in normal dogs after the administration of lidocaine in doses of up to 5 mg/kg. In our study, lidocaine administered in a dose of 2 mg/kg and 4 mg/kg had only a minimal depressant effect on His-Purkinje conduction in normal tissue, reflected by a slight increase in the H-V interval that was significant only at a dose of 4 mg/kg and a pacing rate of 180 beats/min.

Effect of lidocaine after ischemic damage to His-Purkinje system: The effect of lidocaine several days after an experimental ischemic insult to the His-Purkinje system has not, to our knowledge, been previously reported. Rosen et al.[11] studied the effect of lidocaine in 10 patients with arrhythmias in the presence of arteriosclerotic, primary or hypertensive cardiac disease and reported that at various pacing rates lidocaine had no effect on the H-Q interval. Kunkel et al.[12] reported no significant change in the His-Purkinje conduction time or QRS duration in 10 patients with right or left bundle branch block after administration of lidocaine; however, atrial pacing was not performed in their study. Josephson et al.[13] found that lidocaine shortened the effective and relative refractory periods of the His-Purkinje system in 14 patients. However, several investigations[14,15] have reported instances of heart block in patients receiving lidocaine for the treatment of arrhythmias. In addition, Gupta et al.[16] and Roos and Dunning[17] reported transient deterioration of His-Purkinje function after the administration of lidocaine in one third to one half of patients with preexisting conduction system disease.

Our study demonstrates that there is a spectrum of conduction disturbances present after an experimental ischemic insult to His-Purkinje tissue. Some animals have conduction defects that are evident during sinus rhythm and atrial pacing, some have latent conduction defects that are manifest only after the administration of lidocaine, and some have no abnormalities even in the presence of lidocaine and atrial pacing. This "selective" effect of lidocaine—that is, its greater effect in ischemic tissue than in normal cardiac tissue—has previously been demonstrated in Purkinje cells and cardiac muscle in open chest dog studies but not in the intact His-Purkinje system.[3–5] Sasyniuk and Kus[3] reported that, compared with normal Purkinje fibers, subendocardial Purkinje fibers surviving myocardial infarction demonstrated markedly decreased action potential amplitudes and a maximal rate of depolarization of phase 0 in response to lidocaine. Kupersmith et al.[4] described a prolongation in the time from the Q wave to the electrogram recorded over infarcted muscle and an increase in the effective refractory period of the infarct zone in response to lidocaine, in contrast to no effect in normal tissue in the dog 2 hours after myocardial infarction. In addition, El-Sherif et al.[5] demonstrated that lidocaine selectively slowed conduction in reentrant pathways of ischemic cardiac muscle but did not affect conduction in normal muscle. The reason for the selective effect of lidocaine is unclear, although it has been postulated that lower pH in the infarct zone, greater extracell potassium concentration, local metabolic products or depression of the fast sodium channel due to ischemia may be responsible.

Clinical implications: In the dogs in this experiment, lidocaine depressed conduction in His-Purkinje tissue, which had residual latent damage after an ischemic insult. If lidocaine has the same effect in human beings, it could prove useful in evaluating patients with evidence of conduction system disease during a myocardial infarction. It is not uncommon for a patient to have transient heart block or bundle branch block in the coronary care unit. However, the degree of latent conduction system disease in the recovery period, and therefore the need for a pacemaker, is unclear in many instances. In patients with a suspected A-V conduction defect secondary to acute myocardial infarction, the use of His bundle recordings performed during the stress of atrial pacing and lidocaine may identify more precisely those patients with latent disease who are at greater risk of sudden death due to cardiac asystole.

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Anatomic Types of Congenital Mitral Stenosis: Report of 49 Autopsy Cases With Consideration of Diagnosis and Surgical Implications

ROGER N. RUCKMAN, MD*
RICHARD VAN PRAAGH, MD, FACC

Boston, Massachusetts

In a series of 49 autopsy cases of congenital mitral stenosis, four anatomic types were found: (1) typical congenital mitral stenosis with short chordae tendineae, obliteration of interchordal spaces and reduction of interpapillary distance (24 cases, 49 percent); (2) hypoplastic congenital mitral stenosis almost always associated with a hypoplastic left heart syndrome (20 cases, 41 percent); (3) supramitral ring (6 cases, 12 percent); and (4) parachute mitral valve (4 cases, 8 percent). The median ages at death were as follows: parachute mitral valve, 9 11/12 years; supramitral ring, 5 6/12 years; typical congenital mitral stenosis, 6 months, and hypoplastic congenital mitral stenosis, 5 days. Thus, parachute mitral valve had the best natural history and the hypoplastic type of mitral stenosis the worst; that of the other two types was intermediate. Associated malformations were present in 96 percent of cases, endocardial sclerosis or florid endocardial fibroelastosis occurring in 47 percent, hypoplasia of the aortic isthmus in 37 percent, aortic valve stenosis in 29 percent, aortic atresia in 29 percent and coarctation of the aorta in 27 percent of the cases. On the basis of an understanding of the pathologic anatomy, real time two-dimensional echocardiography probably will make it possible to make the differential diagnosis among the four major anatomic types of congenital mitral stenosis. Mitral valvuloplasty of several new types appears to merit trial as the initial surgical procedure. At present, mitral valve replacement should be deferred as long as possible.

With the advent of refinements in echocardiography[1–4] and with improvements of surgical techniques,[5] there has been renewed interest in the diagnosis and treatment of congenital mitral stenosis. This study was undertaken in an effort to clarify the principal pathologic findings of congenital mitral stenosis and to propose an anatomic classification.

Material and Methods

Forty-nine autopsy cases of congenital mitral stenosis from the Children's Hospital Medical Center in Boston were reviewed. Two cases included surgical specimens (supramitral ring). All cardiac anomalies were recorded. Patients who had undergone mitral valve replacement were excluded. The size of the mitral valve orifice was measured at its smallest point, which frequently was the distal end of the mitral cone but in supramitral ring was its proximal end. A calibrated valve sizer was used to make these measurements. Left ventricular size (height) was measured from the apex to the base of the junction of the right and noncoronary aortic valve leaflets. This measurement was found to be more consistent and repeatable than measurement from the mitral valve to the apex or attempted measurement of the perimeter of the left ventricle half way between mitral valve and apex. Measurements were compared with those of age-matched normal control subjects, and expressed as percent of control. Cases with mitral regurg-

From the Department of Cardiology and Pathology, Children's Hospital Medical Center and the Department of Pathology, Harvard Medical School, Boston, Massachusetts. This work was supported in part by Grants HLB5855 and HLB10436 from the National Institutes of Health, Bethesda, Maryland. Manuscript received November 28, 1977; revised manuscript received June 6, 1978, accepted June 7, 1978.

* Present address: Roger N. Ruckman, MD, Department of Pediatrics, Section of Pediatric Cardiology, The University of Nebraska Medical Center, Omaha, Nebraska.

Address for reprints: Richard Van Praagh, MD, Childrens Hospital Medical Center, 300 Longwood Avenue, Boston, Massachusetts 02115.

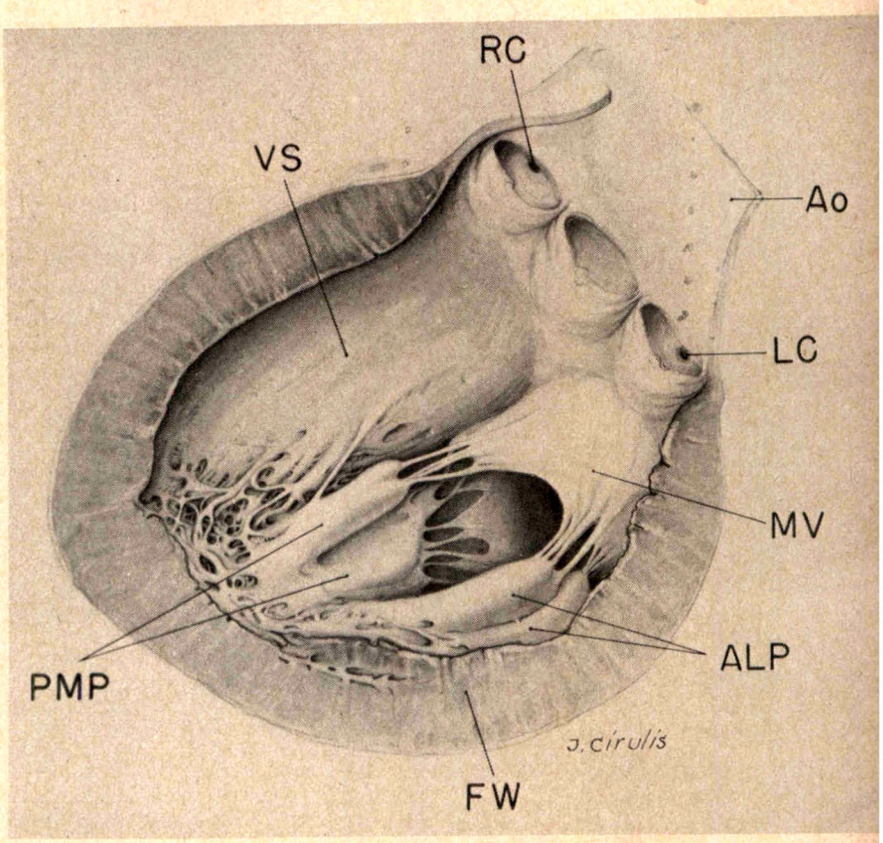


FIGURE 1. Normal mitral valve (MV), open left ventricle and aorta (Ao) (Autopsy no. A65-12). Note that the interpapillary distance is relatively wide between the anterolateral papillary muscle group (ALP) and the posteromedial papillary muscle group (PMP). The chordae tendineae of the mitral valve are relatively long and thin, and the interchordal spaces are well formed. No bands of fibrous tissue run from the anterior leaflet of the mitral valve to the left ventricular septal surface (VS), and there are no aberrant chordal insertions directly into the free wall (FW) of the left ventricle. LC = left coronary artery; RC = right coronary artery.

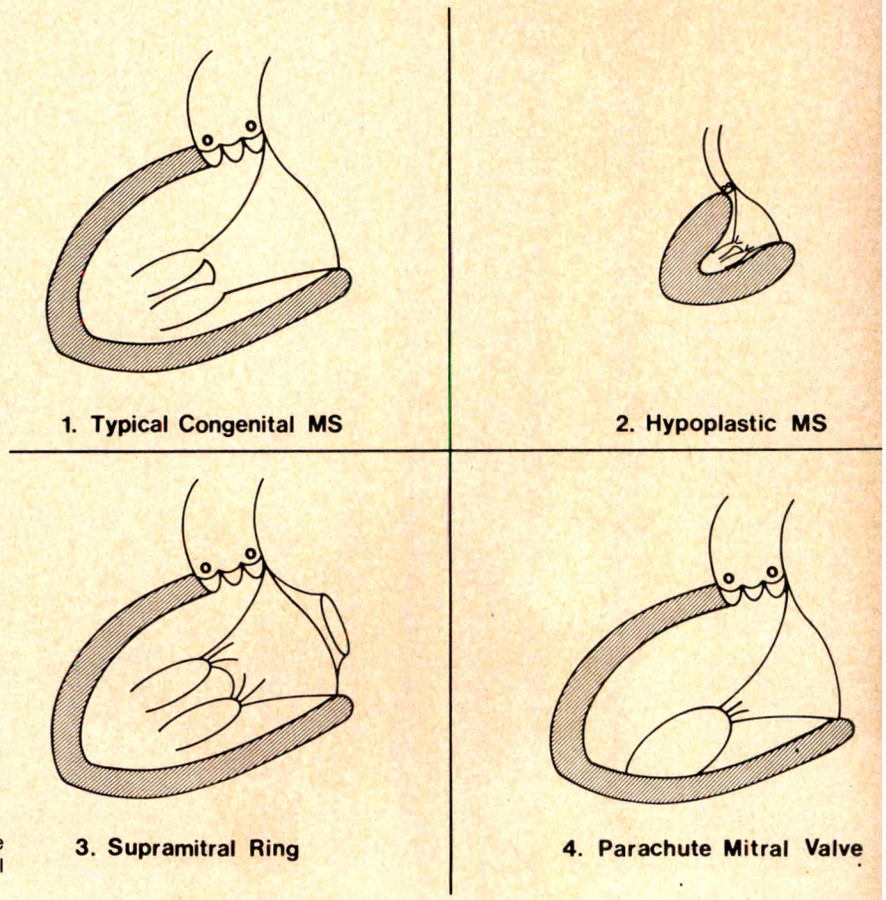


FIGURE 2. Diagrammatic representation of the four major anatomic types of congenital mitral stenosis (MS) found in this series.

TABLE I

Classification and Frequency of 49 Cases of Congenital Mitral Stenosis

Frequency	Type of Congenital Mitral Stenosis	Cases (no.)	Percent of Series
1	Typical	24	49
2	Hypoplastic	20	41
3	Supramitral ring	6†	12†
4	Parachute mitral valve	4*	8*
	Totals	54‡	110‡

* Two cases of parachute mitral valve also had supramitral ring (Cases 47 and 48). One case of parachute mitral valve is a forme fruste (Case 17).

† Two cases had both supramitral ring and typical congenital mitral stenosis (Cases 2 and 21).

‡ Two cases had both parachute mitral valve and supramitral ring; two cases had both supramitral ring and typical congenital mitral stenosis.

itation that did not show at least 15 percent narrowing of effective mitral valve orifice compared with control measurements were excluded.

Findings

The median age at death in the 49 cases was 2 months (range 1 day to 28 years). There was a male predominance, with a male/female ratio of 1.5/1.

The relative frequency of the various types of mitral stenosis is presented in Table I. Congenital mitral stenosis was classified in terms of the configuration of the tensor apparatus in relation to the valve leaflets (Fig. 1). In the majority of the 49 cases (47 cases, 96 percent) the congenital mitral stenosis was associated with other congenital heart disease. The associated defects seen with each type of congenital mitral stenosis are summarized in Tables II to VII.

TABLE II

Typical Congenital Mitral Stenosis (nine cases)

Case no.	Autopsy no.	Age at Death	Associated Lesions	Mitral Orifice Size (% of normal)	Left Ventricular Size (% of normal)
1	A51-294	3 wk	Aortic stenosis, endocardial sclerosis, double chamber right ventricle	80	100
2	A54-178	5 6/12 yr	Tetralogy of Fallot, supramitral ring	46	100
3	A60-268	4 wk	Coarctation of aorta, patent ductus arteriosus	87	107
4	A63-6	4 mo	Subaortic stenosis, coarctation of the aorta, cleft tricuspid valve, ventricular septal defect (canal type)	63	106
5	A63-204	28 yr	Coarctation of aorta, aortic regurgitation	80	136
6	A64-75	4 wk	Aortic stenosis, coarctation of aorta, patent ductus arteriosus	81	75
7	A65-231	15 yr	Ebstein's anomaly, small right ventricle	63	142
8	A63-134	9 yr	Aortic stenosis, coarctation of aorta (status post repair), endocardial sclerosis, mitral regurgitation	84	100
9	C68-213	4 mo	. . .	69	100

TABLE III

Typical Congenital Mitral Stenosis With Abnormal Mitral Valve Attachment (eight cases)

Case no.	Autopsy no.	Age at Death	Associated Lesions	Mitral Orifice Size (% of normal)	Left Ventricular Size (% of normal)
10	A57-281	3 5/12 yr	Mitral regurgitation, ventricular septal defect (canal type)	70	170
11	A58-23	7 mo	Aortic stenosis, coarctation of aorta, aberrant left subclavian artery	68	100
12	A58-261	3 mo	Common atrium, coarctation of aorta, patent ductus arteriosus, left superior vena cava to coronary sinus	48	83
13	A59-175	10 mo	Subaortic stenosis, coarctation of aorta, isthmus hypoplasia, patent ductus arteriosus, ventricular septal defect (conoventricular)	56	75
14	A64-19	3 1/2 mo	Aortic stenosis, coarctation of aorta, isthmus hypoplasia, endocardial sclerosis, patent ductus arteriosus	80	106
15	A65-10	3 1/2 mo	Mitral septal cord, small left ventricle, mitral regurgitation, patent ductus arteriosus	80	76
16	A69-56	5 2/12 yr	Subaortic stenosis, small right ventricle, mitral regurgitation	73	100
17	A74-205	2 mo	Parachute mitral valve (forme fruste), tetralogy of Fallot, small left ventricle	72	70

TABLE IV

Typical Congenital Mitral Stenosis With Loss of Interpapillary Distance (seven cases)

Case no.	Autopsy no.	Age at Death	Associated Lesions	Mitral Orifice Size (% of normal)	Left Ventricular Size (% of normal)
18	A62-71	2 1/12 yr	Subaortic stenosis, patent ductus arteriosus	58	100
19	A67-236	6 mo	Tetralogy of Fallot, endocardial sclerosis	56	94
20	A68-168	4 1/2 mo	Subaortic stenosis, tetralogy of Fallot, small left ventricle, left superior vena cava to coronary sinus	70	70
21	A70-136	2 10/12 yr	Supramitral ring, ventricular septal defect (muscular and conoventricular, status post repair), left superior vena cava to coronary sinus	59	90
22	A71-164	1 8/12 yr	Subaortic stenosis, tetralogy of Fallot, endocardial sclerosis (left atrium)	73	97
23	A72-191	2 days	Aortic stenosis, endocardial sclerosis, patent ductus arteriosus	60	90
24	A73-154	4 days	Aortic stenosis, patent ductus arteriosus	60	90

TABLE V

Hypoplastic Congenital Mitral Stenosis (20 cases)

Case no.	Autopsy no.	Age at Death	Associated Lesions	Mitral Orifice Size (% of normal)	Left Ventricular Size (% of normal)
25	A58-262	5 days	Aortic atresia, small left ventricle, endocardial fibroelastosis, hypoplastic isthmus, patent ductus arteriosus, atrial septal defect (secundum), aneurysm of septum primum	66	60
26	A59-134	42 days	Aortic stenosis, endocardial fibroelastosis, patent ductus arteriosus, patent foramen ovale	66	73
27	A59-333	11 1/12 yr	Aortic stenosis, endocardial fibroelastosis, coarctation of aorta, hypoplastic isthmus, patent ductus arteriosus	40	77
28	A63-81	32 days	Aortic stenosis, endocardial fibroelastosis, patent ductus arteriosus	73	71
29	A68-228	12 days	Aortic stenosis, small left ventricle, endocardial fibroelastosis, hypoplastic isthmus, patent ductus arteriosus	20	43
30	A69-6	11 days	Aortic atresia, small left ventricle, endocardial fibroelastosis, hypoplastic isthmus, patent ductus arteriosus, atrial septal defect (secundum), sinus septal defect, small left atrium	20	36
31	A69-269	3 days	Aortic stenosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus, atrial septal defect (primum)	30	35
32	A71-175	3 days	Aortic atresia, small left ventricle, endocardial fibroelastosis, hypoplastic isthmus, patent ductus arteriosus	30	50
33	A73-37	2 days	Aortic atresia, small left ventricle, endocardial fibroelastosis, hypoplastic isthmus, patent ductus arteriosus	30	50
34	A55-124	3 days	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus	29	20
35	A63-305	3 days	Aortic atresia, small left ventricle, patent ductus arteriosus, left superior vena cava to coronary sinus	29	50
36	A67-34	3 days	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus, small left atrium	29	50
37	A67-200	14 days	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus, small coronary arteries (diminished caliber)	20	43
38	A68-72	21 days	Aortic stenosis, coarctation of aorta, hypoplastic isthmus, atrial septal defect (secundum)	39	89
39	A69-97	58 days	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus	21	29
40	A69-168	42 hr	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus, atrial septal defect (secundum)	48	50
41	A70-41	3 days	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus, atrial septal defect (secundum)	48	40
42	A70-228	36 hr	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus, small left atrium	30	40
43	A71-268	7 days	Aortic atresia, endocardial fibroelastosis, small left ventricle, hypoplastic isthmus, patent ductus arteriosus	60	60
44	A72-16	65 hr	Aortic atresia, endocardial fibroelastosis, small left ventricle, patent ductus arteriosus, small left atrium	30	40

TABLE VI

Supramitral Ring (six cases)

Case no.	Autopsy no.	Age at Death	Associated Lesions	Mitral Orifice Size (% of normal)	Left Ventricular Size (% of normal)
2	A54-178	5 6/12 yr	Tetralogy of Fallot, typical congenital mitral stenosis	46	100
21	A70-136	2 10/12 yr	Typical congenital mitral stenosis, left superior vena cava, ventricular septal defect (muscular and conoventricular, status post repair)	59	90
45	A53-159	4 1/2 mo	Small left ventricle	47	65
46	A60-113	10 6/12 yr	(Resection of supramitral ring performed 5 months before death)	100	133
47	A70-173	5 7/12 yr	Aortic stenosis, infundibular pulmonary stenosis, coarctation of aorta, parachute mitral valve, ventricular septal defect (conoventricular)	58	100
48	A75-62	14 3/12 yr	Coarctation of aorta, parachute mitral valve, ventricular septal defect (membranous) (resection of supramitral ring and valvotomy performed 9 months before death)	130	108

TABLE VII

Parachute Mitral Valve (four cases)

Case no.	Autopsy no.	Age at Death	Associated Lesions	Mitral Orifice Size (% of normal)	Left Ventricular Size (% of normal)
17	A74-205*	2 mo	Tetralogy of Fallot, small left ventricle	72	70
49	A63-280	20 yr	(Valvotomy performed 12 yr before death)	84	136
47	A70-173	5 7/12 yr	Aortic stenosis, infundibular pulmonary stenosis, coarctation of aorta, supramitral ring, ventricular septal defect (conoventricular)	58	100
48	A75-62	14 3/12 yr	Coarctation of aorta, ventricular septal defect (membranous), supramitral ring (resection of supramitral ring and valvotomy performed 9 months before death)	130	108

* Variant (that is, both papillary muscles present with only posteromedial papillary muscle accepting chordal attachments).

In comparison with the normal mitral valve (Fig. 1), the valve with congenital mitral stenosis represented a spectrum of anomalies involving the mitral anulus, the leaflets, the chordae tendineae and the papillary muscles. Four anatomic types were found (Fig. 2). Each case showed narrowing of the effective mitral valve orifice. Abnormal left atrioventricular (A-V) flow patterns, including interchordal flow (through interchordal spaces) or interleaf flow (between the two leaflets), or both, would be expected with all four types of congenital mitral stenosis (Fig. 3 to 7).

Typical Congenital Mitral Stenosis (24 cases)

"Typical" congenital mitral stenosis (nine cases, Table II): By this term we mean what is usually reported as "congenital mitral stenosis." Descriptions of this entity have emphasized mitral obstruction within the leaflets or their chordal support in association with a functioning left ventricle.[6–9] In typical congenital mitral stenosis (Fig. 3), the leaflet margins are thickened and rolled, the chordae tendineae are shortened and thickened, the interchordal spaces are partially or completely obliterated by fibrous tissue, the papillary muscles are underdeveloped and the interpapillary distance is mildly reduced.

Only one case of isolated typical congenital mitral stenosis was identified (Fig. 3). The most common associated lesions were coarctation of the aorta (five of nine cases, 56 percent) and aortic stenosis (three cases, 33 percent). Overall, one or more of the anomalies were seen in 67 percent of the patients with typical congenital mitral stenosis. One of these patients showed evidence of mitral regurgitation: jet lesions of the left atrial endocardium and rolling of the free margins of the mitral leaflets. The shortening of the chordae tendineae and leaflet thickening appeared to have prevented proper coaptation of the mitral leaflets during systole. This patient, who had undergone prior repair of coarctation but had not had mitral valve surgery, had a significantly longer survival time than the median for the group as a whole.

The hearts with typical congenital mitral stenosis also showed focal left ventricular endocardial sclerosis. The left ventricular size was normal or only mildly reduced (greater than 70 percent of control size) in all of these patients (Table II). The size of the effective mitral valve orifice showed at least 15 percent narrowing (orifice less than 85 percent of control size) in 89 percent of cases. All cases showed reduced interchordal spaces. Neither the size of the left ventricle nor that of the mitral orifice correlated with survival time. The median age at death in this group was 2 11/12 years.

Two subtypes within the category of typical congenital mitral stenosis had anatomic features that are sufficiently distinctive to merit separate description.

Abnormal mitral valve attachment (eight cases, Table III): This form of mitral stenosis involves an abnormality of the tensor apparatus. One or more chordae tendineae may insert directly into the left ventricular free wall or septal surface, or the mitral leaflets may attach virtually directly into the papillary muscles with little or no intervening chordae. The result is not only reduced leaflet mobility but often a tendency to poor leaflet coaptation in systole with resultant mitral regurgitation. Evidence of mitral regurgitation was noted in three of these eight cases. Other associated anomalies included coarctation of the aorta (four cases)

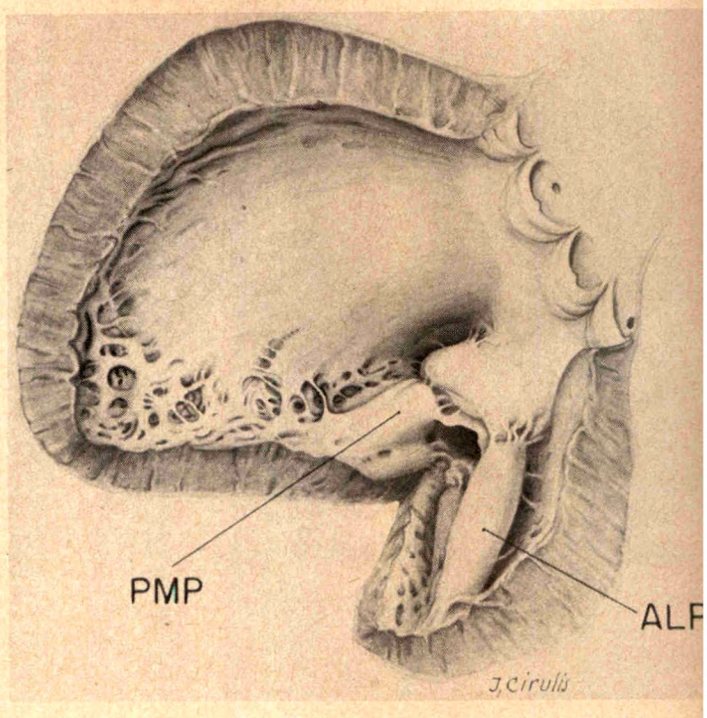


FIGURE 3. Case 9. Typical congenital mitral stenosis (Table II). The interpapillary distance between the anterolateral (ALP) and the posteromedial (PMP) papillary muscle groups is mildly reduced. The chordae tendineae are shortened and the interchordal spaces are obliterated with fibrous tissue. The thickened anterior mitral leaflet bulges into the left ventricular cavity, which is normal in size. In typical congenital mitral stenosis, abnormal left atrioventricular flow and pressure result from a combination of reduced interleaflet, interchordal and interpapillary flow.

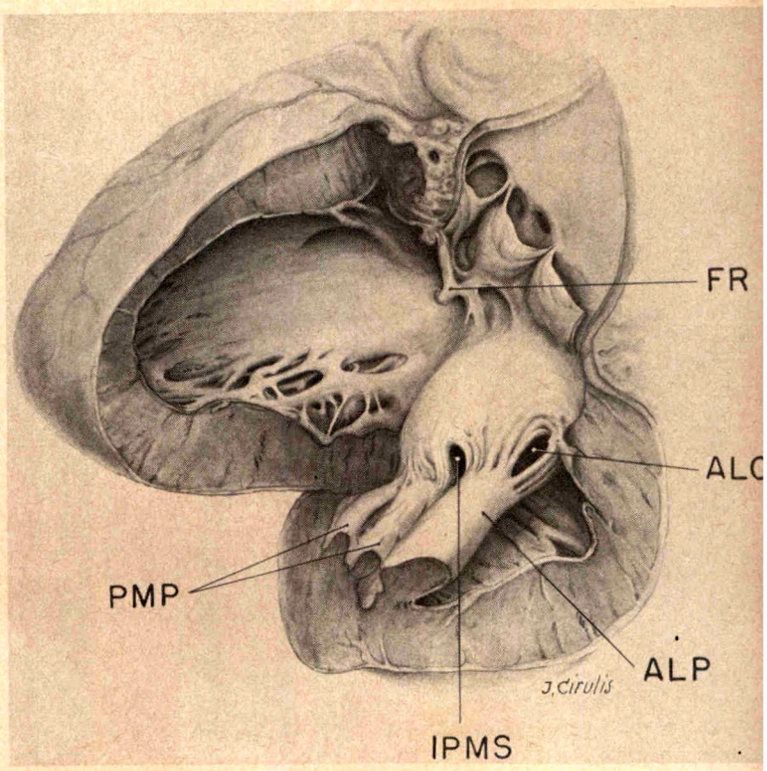


FIGURE 4. Case 18. Typical congenital mitral stenosis with marked reduction of the space between the anterolateral (ALP) and the posteromedial (PMP) papillary muscle groups, which are identifiable but fused (Table IV). This is not considered an example of parachute mitral valve because both papillary muscle groups are present and both receive insertions from the shortened and thickened chordae tendineae, but the anomaly may be regarded as a forme fruste of parachute mitral valve. The mitral valve orifice is markedly reduced; there is only one small opening above the interpapillary muscle space (IPMS) and another small aperture at the anterolateral commissure (ALC). Note the physiologically insignificant subaortic fibrous ring (FR) extending from the anterior mitral leaflet onto the left ventricular septal surface beneath the aortic valve.

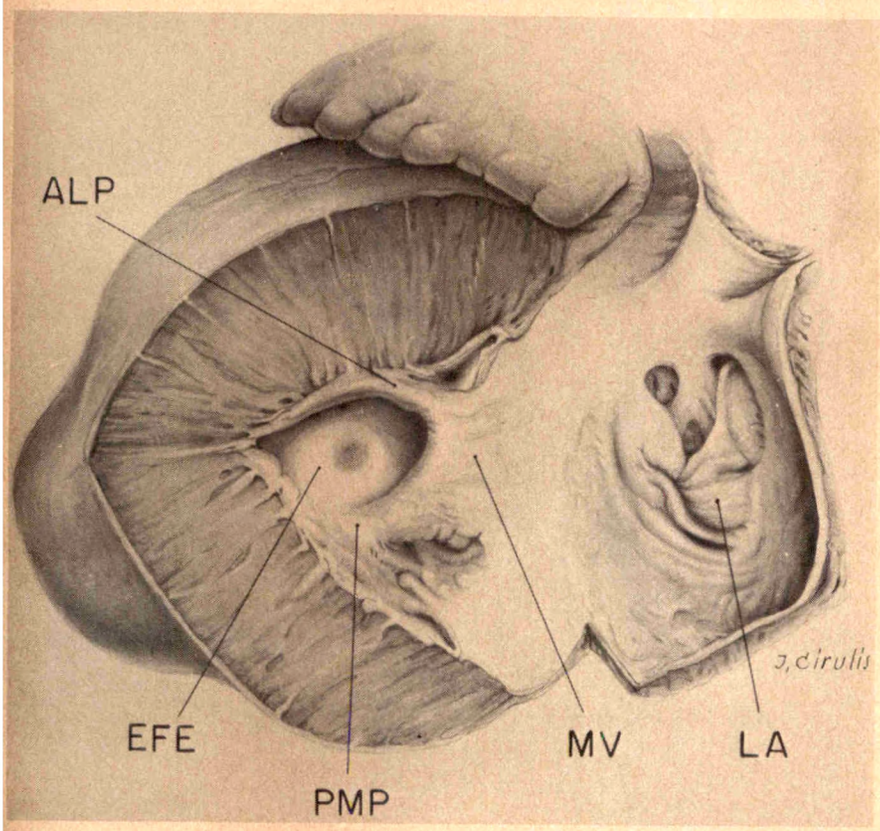


FIGURE 5. Case 29. The hypoplastic type of congenital mitral stenosis found in a case of severe congenital aortic stenosis with an intact ventricular septum and severe endocardial fibroelastosis (EFE) of the left ventricle (Table V). The small left ventricular cavity, the relatively thick left ventricular free wall, the atrophy of the anterolateral (ALP) and the posteromedial (PMP) papillary muscle groups and the absence of interchordal spaces are noteworthy. The free margin of the mitral valve (MV) is conspicuously thickened and rolled, forming a congenital mitral arcade. The hypertrophy and enlargement of the left atrium (LA) are well shown. This was the most severe example of the hypoplastic type of congenital mitral stenosis found in this series.

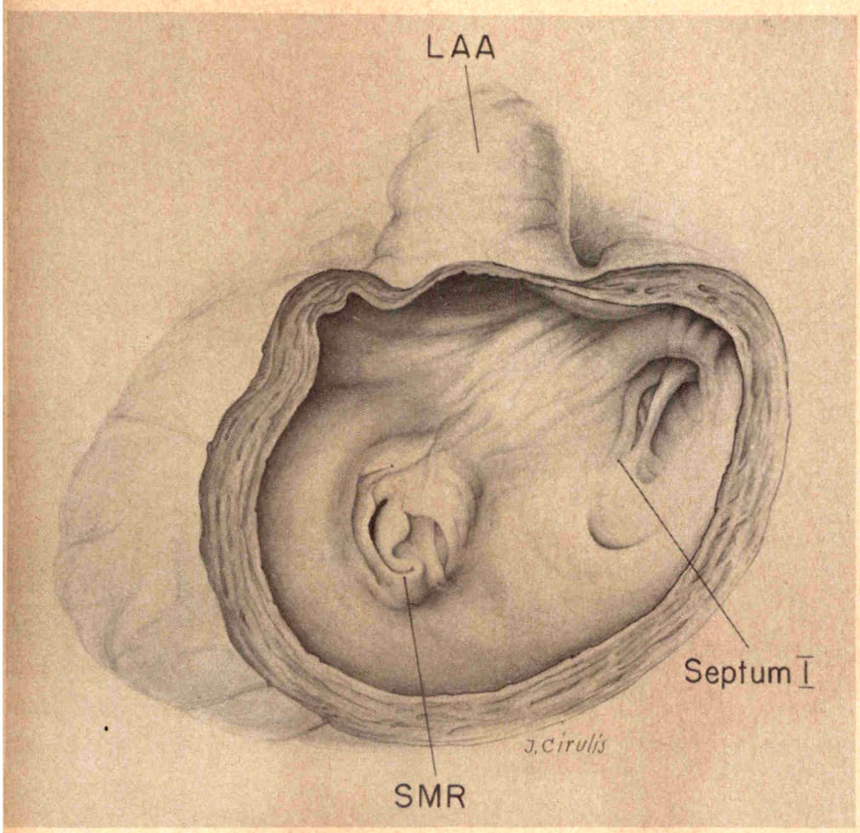


FIGURE 6. Case 2. Supramitral ring (SMR) producing severe congenital mitral stenosis (Table VI). Note the marked hypertrophy and enlargement of the left atrium and left atrial appendage (LAA). This supramitral ring was associated with typical congenital mitral stenosis of a mild degree and tetralogy of Fallot. The septum primum (Septum I) sealed the foramen ovale, as is typical with left atrial hypertension.

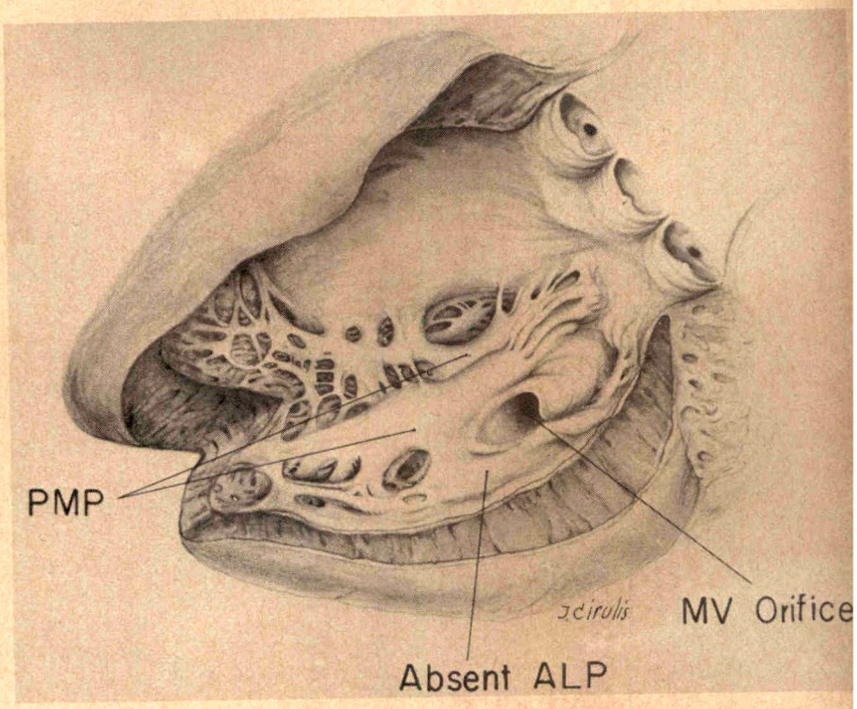


FIGURE 7. Case 49. Parachute mitral valve (Table VII). The anterolateral papillary (ALP) muscle group is absent. The posteromedial papillary (PMP) muscle group is enlarged. All of the thickened chordae tendineae insert into the enlarged posteromedial papillary muscle group, which may be likened to a man on a parachute. The orifice of the mitral valve (MV) is both stenotic and eccentric, opening abnormally laterally and inferiorly into the left ventricular free wall.

aortic stenosis (two cases) and subaortic stenosis (two cases). The median age at death was 5 months. All 8 patients had a left ventricular size that was at least 70 percent of that of age-matched control subjects. Mitral orifice size did not correlate closely with survival time.

Loss of interpapillary distance (seven cases, Table IV): Reduction of the interpapillary distance was occasionally striking, the papillary muscles being close together or fused (Fig. 4). This anomaly could be regarded as intermediate between typical congenital mitral stenosis and parachute mitral valve.[10] All of these patients had normal or mildly reduced left ventricular size and all had reduction of the effective mitral orifice size to less than 85 percent of normal. The median age at death was 6 months. Survival could not be predicted from left ventricular or mitral orifice size. The most common associated abnormalities in the seven cases were subaortic stenosis (three cases), tetralogy of Fallot (three cases) and aortic stenosis (two cases). One patient who underwent successful ventricular septal defect closure and had prolonged survival also had a supramitral ring. No patient had evidence of mitral regurgitation.

Hypoplastic Mitral Stenosis (20 cases, Table V)

The hypoplastic mitral valve (Fig. 5) was the second most frequently observed abnormality in the series (20 cases, 41 percent) (Table I). The mitral valve orifice was small. The chordae tendineae were shortened but usually not thickened and the papillary muscles were small. Interpapillary distance was maintained (relative to the small mitral valve and left ventricle). This type of mitral valve abnormality was distinguished from the normal mitral valve (Fig. 1) by the finding that all components of the valve were in miniature. This form of mitral stenosis was associated with severe left ventricular outflow tract abnormalities in all cases. Aortic stenosis (6 cases, 30 percent) or atresia (15 cases, 75 percent) was found in all. A small left ventricular size was noted in 16 cases (80 percent). A small atrial orifice was also observed in all cases.

The median age at death was 5 days. When the size of the left ventricle was less than 70 percent of control values, survival was less than 28 days in more than 90 percent of cases (Table V). The majority of patients with values greater than 70 percent survived beyond 28 days. However, the overall survival was not a linear function of left ventricular or mitral orifice size.

Hypoplastic left heart syndrome: Previous reviews[8,11,12] have classified the hypoplastic type of congenital mitral stenosis as part of the "hypoplastic left heart syndrome."[13] There is considerable anatomic variation within this syndrome, including variability of the size of the left ventricle and mitral valve. Cases with aortic stenosis tend to have a larger left ventricular size than those with aortic atresia (Table V). Survival is also variable. As noted in our series, a hypoplastic mitral valve can be associated with survival up to 11 years. However, the majority of patients, as is the experience with the "hypoplastic left heart syndrome," die within the first few weeks of life. The hypoplastic form of congenital mitral stenosis is included in this review in the interest of completeness. The primary diagnosis in such patients usually is "hypoplastic left heart syndrome" or aortic stenosis or atresia, hypoplastic con-

genital mitral stenosis almost always being only part of a larger picture, seldom the primary diagnosis.

Supramitral Ring (six cases, Table VI)

Supramitral ring[12,14–16] is a circumferential ridge of connective tissue that originates at the atrial surfaces of the mitral leaflets and causes various degrees of obstruction of the mitral inlet (Fig. 6). This abnormality was usually associated with other abnormalities of the mitral apparatus, especially parachute mitral valve and typical congenital mitral stenosis (each found in two of the six cases in this series). Coarctation of the aorta was also commonly associated. The complex of supramitral ring, parachute mitral valve, subaortic stenosis and coarctation of the aorta[16] was not seen in this series. Of our patients with supramitral ring, longevity correlated with left ventricular size (Table VI). Mitral orifice size (excluding two cases studied after resection of supramitral ring) was variable and did not correlate with longevity. No case of an extremely obstructive supramitral diaphragm was found. The median age at death in this group was 5 7/12 years.

Parachute Mitral Valve (four cases, Table VII)

In parachute mitral valve, all of the chordae tendineae insert into a single papillary muscle group (Fig. 7). The chordae were usually shortened and thickened. The mobility of the valve leaflets was reduced and the effective mitral orifice was decreased. The anterolateral papillary muscle was usually missing. However, the arrangement of papillary muscles, as noted here and in previous reports, was variable.[9,10,12,16–19] For example, in one patient (Case 17, Tables III and VII) both papillary muscles were present but all chordae attached to the posteromedial papillary muscle. Cases with chordal attachments to each of two fused but identifiable papillary muscles were excluded from the category of parachute mitral valve.[20]

Associated anomalies were common with parachute mitral valve. In this series, supramitral ring and coarctation of the aorta were noted in half the cases. Right ventricular outflow obstruction, as noted in Case 17, has also been noted previously.[19] As in cases of supramitral ring, longevity correlated with left ventricular size. In our series, all patients with a left ventricular size at least 70 percent of control value survived beyond the 1st month of life. Mitral orifice size did not correlate with longevity. The median age at death in this group was 9 11/12 years.

Discussion

This is the largest review of the pathologic anatomy of congenital mitral stenosis published to date and the first time that this anomaly has been analyzed using age-matched control hearts for measurement in each case.

Classification: An anatomic classification of congenital mitral stenosis emerged from this study of 49 autopsy cases that we hope will prove helpful and comparatively easy to remember.

1. *Typical congenital mitral stenosis,* with short chordae tendineae, obliteration of interchordal spaces by fibrous tissue, and variable reduction of interpapillary distance (Fig. 3 and 4).
2. *Hypoplastic congenital mitral stenosis,* almost always associated with the hypoplastic left heart syndrome (Fig. 5).
3. *Supramitral ring,* with or without other types of congenital mitral stenosis (Fig. 6).
4. *Parachute mitral valve* (Fig. 7).

Natural history: Associated anomalies are of great importance in determining the course of congenital mitral stenosis. Only three cases of isolated congenital mitral stenosis were noted in this series. All other cases had outflow obstruction (right or left), distal shunt or shunt plus obstruction.

Patients with typical congenital mitral stenosis showed the greatest longevity when outflow obstruction was the major associated anomaly. Patients with left-sided obstruction (median age at death 4 1/2 years) had a shorter survival time than those with right-sided obstruction (median age at death 10 3/12 years). Lack of associated anomalies did not necessarily prolong survival (Case 9, Table II). The shortest survival time occurred in patients with shunt plus obstruction (median age at death 3 1/2 months). Those with abnormal mitral valve attachment (Table III) also had the shortest survival time when there was a shunt plus obstruction (median age at death 3 1/2 months).

Patients with the hypoplastic type of congenital mitral stenosis, as a group, showed outflow obstruction. Only one (Case 38, Table V) had no associated shunt. This patient had prolonged survival relative to the median for the group.

Supramitral ring and parachute mitral valve occurred in too few cases for analysis by associated anomalies. Lack of associated anomalies did not necessarily prolong survival in patients not operated on (Case 45, Table VI).

This study also represents the first attempt to correlate longevity with the anatomic types of congenital mitral stenosis and with the sizes of the mitral valve and of the left ventricle. Patients with parachute mitral valve and supramitral ring had the greatest longevity, the median ages at death being 9 11/12 years and 5 6/12 years, respectively. Those with the hypoplastic form had the shortest survival time, the median age at death being only 5 days. Patients with typical congenital mitral stenosis had intermediate longevity, the median age at death being 6 months. Patients with supramitral ring and parachute mitral valve with a relatively large left ventricular size tended to show longer survival. In all four types of congenital mitral stenosis, survival was principally determined by the associated anomalies.

Diagnosis—the role of echocardiography: The presence of certain frequently associated anomalies such as coarctation of the aorta has, by inference, provided indirect evidence for the presence of congenital mitral valve disease of various types.[10,21] Direct evidence for congenital mitral stenosis has been difficult to obtain. In a large clinical series from this institution,[22] symptoms and chest X-ray, electrocardiographic and vectorcardiographic findings were variable. Even with satisfactory angiocardiograms, the diagnosis was not established in 10 of 36 cases. M mode echocardiography has been helpful in some cases[1–4] but does not allow visualization of the size or number of papillary muscles.

Real time two-dimensional echocardiography may well make it possible to diagnose accurately the various anatomic types of congenital mitral stenosis.

Typical congenital mitral stenosis may be identified by the reduction of the interpapillary distance in the transverse apical view. This form may or may not display abnormal bands between the anterior mitral leaflet and left ventricular septal surface, or abnormal chordal insertions into the left ventricular free wall.

The hypoplastic type of congenital mitral stenosis can be identified by the small left ventricular cavity size and by the associated aortic atresia or severe stenosis.[4]

Parachute mitral valve should prove definitely recognizable using two dimensional echocardiography by demonstrating the presence of only one papillary muscle group in the transverse apical view. The sagittal view should show all chordae inserting into one papillary muscle group, with reduction of leaflet excursion.

Supramitral ring has been accurately diagnosed echocardiographically.[2,4]

Surgery—role of plastic reconstructive procedures and mitral valvuloplasty: New plastic reconstructive procedures[5] on the mitral valve may prove to be applicable to typical congenital mitral stenosis when all tensor structures are present. The hypoplastic type of congenital mitral stenosis may or may not be amenable to surgical therapy, depending on the type of hypoplastic left heart syndrome that coexists and its severity. Parachute mitral valve may perhaps be treatable with a plastic reconstructive approach.[5] However, absence of one papillary muscle group in parachute mitral valve probably would make a plastic approach more difficult than in typical congenital mitral stenosis, in which none of the tensor apparatus is missing. The supramitral ring type of congenital mitral stenosis can now be treated successfully with resection.[23]

Many patients with congenital mitral stenosis may ultimately require mitral valve replacement. One great advantage of mitral valvuloplasty as the initial surgical procedure in congenital mitral stenosis is that it postpones mitral valve replacement until the patient and the heart are larger; it might even obviate later mitral valve replacement. Mitral valve replacement should be postponed as long as possible to minimize iatrogenic mitral stenosis associated with the smaller prostheses and to avoid left ventricular outflow tract obstruction produced by the ring and, in tissue valves, also by the struts of the mitral valve prosthesis. Left ventricular cavity size in this series of congenital mitral stenosis was small (less than or equal to 70 percent of normal control measurements) in 19 of the 49 cases (39 percent).

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Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy in the Presence of Right Bundle Branch Block in Young Subjects

CHRISTIAN R. BROHET, MD*
MADY STYNS, MD†
PIERRE ARNAUD, MD‡
LUCIEN A. BRASSEUR, MD*

Brussels, Belgium
Lyon, France

Two groups of young patients, one with right bundle branch block complicated by right ventricular hypertrophy due to congenital heart disease, the other with right bundle branch block and no right ventricular hypertrophy, could be separated on the basis of a few quantitative vectorcardiographic and electrocardiographic criteria. Vectorcardiographic criteria proved better than electrocardiographic criteria in detecting right ventricular hypertrophy in individual patients with complete right bundle branch block. Criteria based on the configuration of the QRS loop were also specific but much less sensitive for the diagnosis of this association.

In a similar population, that is, young patients with postoperative right bundle branch block, the existence of a residual right ventricular overload would be strongly suggested by the presence of any one of the following criteria: (1) a clockwise rotation of the QRS loop in the horizontal plane, (2) a ratio of the magnitude of the R wave to that of the S wave (R/S ratio) in lead X at less than 2.0, (3) a mean QRS vector in lead X more negative than −10 mv·msec, or (4) a maximal QRS vector located between 90° and 270° in the horizontal plane. In contrast, an R/S ratio in lead X that was equal or superior to 2.0 or an azimuth angle of the mean spatial QRS vector that was not between 90° and 180° would indicate that the right ventricular conduction defect is probably uncomplicated.

When right ventricular hypertrophy is associated with right bundle branch block, the electrocardiographic diagnosis of both conditions may be difficult.[1,2] The right bundle branch block is responsible for modifications that can completely obscure the signs of concomitant right ventricular hypertrophy.[3] On the other hand, conditions leading to a diastolic overload of the right ventricle can mimic all the features of incomplete or even complete right bundle branch block.[4,5] This study was undertaken to investigate distinguishing features of right ventricular hypertrophy in the presence of complete right bundle branch block.

Recent reports demonstrated the value of the vectorcardiogram in detecting atypical or complicated right bundle branch block such as that found in patients with heart failure or pulmonary disease.[6,7] The proposed criteria were almost exclusively based on morphologic patterns; that is, the degree of anterior displacement of the middle part of the QRS loop in the transverse plane would reflect the importance of right ventricular hypertrophy superimposed on the right ventricular conduction defect. However, other reports have indicated the drawbacks of this approach; that is, the same configuration of the QRS loop in the transverse plane can be seen in other conditions,[8–10] and some investigators[11,12] believe that it can also occur in cases of isolated uncomplicated right bundle branch block.

In this study, adopting a more global approach to the analysis of the vectorcardiogram, we used both qualitative and quantitative criteria for the diagnosis of this association. In addition to electrophysiologic con-

From the Cardio-Pulmonary Laboratory, Department of Medicine,* and the Department of Pediatric Cardiology,† University of Louvain Hospitals, Brussels, Belgium, and the Institut National de la Santé et de la Recherche Médicale U121-Hôpital Cardio-vasculaire,‡ Lyon, France. Manuscript received January 31, 1978; revised manuscript received May 15, 1978, accepted May 17, 1978.

Address for reprints: Christian R. Brohet, MD, Université Catholique de Louvain, Box 5550, Avenue Hippocrate 55, 1200, Brussels, Belgium.

cerns, the study also attempted to assess whether one can rely on the vectorcardiogram to diagnose residual right ventricular hypertrophy in the presence of postoperative right bundle branch block.

Material and Methods

Case Material

A nearly experimental model was provided by a series of 46 patients with congenital heart disease who had surgically induced right bundle branch block added to previously known right ventricular hypertrophy, for example, after correction of tetralogy of Fallot or a ventricular septal defect with pulmonary hypertension or pulmonary valve stenosis. Right bundle branch block was also found in two patients with an atrial septal defect of the ostium secundum type and documented right ventricular overload. No patient with an ostium primum atrial septal defect or other kind of endocardial cushion defect was included. The vectorcardiograms of these 48 patients were then analyzed and compared with those of a control group of 25 subjects with "isolated" right bundle branch block, that is, without evidence of right ventricular overload on hemodynamic study (22 subjects) or clinical data (3 subjects).

The patients were from two centers: One group, from the Cardio-Vascular Hospital of Lyon, France, consisted of 11 patients with isolated right bundle branch block and 10 with right bundle branch block and right ventricular hypertrophy; the second group, from the Department of Pediatric Cardiology of the University of Louvain Hospitals, Belgium, consisted of 14 patients with isolated and 38 with combined right bundle branch block and right ventricular hypertrophy.

TABLE I

Composition of the Clinical Groups

Group	Age Range and Mean	Clinical Criteria	Cases (no.)
Group A (no. = 14): right bundle branch block and "pure" right ventricular hypertrophy	10 mo to 16 yr (mean 4.6 yr)	1. Tetralogy of Fallot without previous palliative L → R anastomosis; VCG recorded in:	
		A. Early postoperative period (within 1 month)	11
		B. Late postoperative period, with hemodynamic and angiographic evidence of residual right ventricular overload	1
		2. Nonsurgical RBBB with RVH: large atrial septal defect, ostium secundum type, with systolic and diastolic overload of the right ventricle (increased pressure and flow)*	2
Group B (no. = 34): right bundle branch block and "mixed" right ventricular hypertrophy (associated left to right shunt at ventricular or arterial level)	5 mo to 11 yr (mean 4.5 yr)	1. Tetralogy of Fallot with L → R anastomosis	
		A. Previous L → R anastomosis and early postoperative period	11
		B. Previous L → R anastomosis, late postoperative period and evidence of residual right ventricular hypertrophy	2
		C. Large ventricular septal defect: bidirectional shunt and pulmonary over systemic blood flow ratio >1.2, early postoperative period	2
		2. Ventricular septal defect and hemodynamic evidence of right ventricular overload (right ventricular work increased by 25%: high pressure and flow), or perioperative verification of right ventricular hypertrophy, or both. VCG recorded in:	
		A. Early postoperative period (within 1 month)	17
		B. Late postoperative period (later than 1 month) with hemodynamic and angiographic evidence of residual right ventricular overload	2
Group C (no. = 25): right bundle branch block without right ventricular hypertrophy	1 yr to 28 yr (mean 10.6 yr)	1. No cardiac abnormality	4
		2. Atrial septal defect of ostium secundum type, small size, with only slight diastolic right ventricular overload (normal pressure)	2
		3. Ventricular septal defect with normal right ventricular pressure and flow	5
		4. Various congenital abnormalities without right ventricular overload	6
		5. Surgical RBBB after closure of a ventricular septal defect (normal right ventricular pressure and flow at the hemodynamic control study)*	4
		6. Surgical RBBB after correction of tetralogy of Fallot, with absence of RVH at the hemodynamic and angiographic control study*; normal right ventricular pressure and flow, no residual gradient, normal wall thickness and normal cavity size; duration of follow-up 1 to 7 years (mean 3 years)	4

*Vectorcardiographic and hemodynamic studies performed within the same week.
L → R = left to right; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; VCG = vectorcardiogram.

On the basis of independent criteria collected from hemodynamic and angiographic studies and from perioperative observations, the 73 patients were classified into three clinical groups (groups A, B and C) that are described in detail in Table I. A preliminary study revealed no substantial differences in vectorcardiographic pattern among various sites of block of the right bundle.[13] Therefore, in this study all the records were analyzed without differentiating between surgical and nonsurgical right bundle branch block.

The diagnosis of right bundle branch block was based on two criteria: (1) a total QRS duration of more than 90 msec in children, and (2) the vectorcardiographic evidence of a delayed terminal "appendage" of the QRS loop directed anteriorly and to the right in the transverse plane. Throughout this paper, we use the general term "right bundle branch block," without making any assumption about the exact site of the conduction defect, and the term "right ventricular hypertrophy," whether the anatomic substratum is increased wall thickness or an enlarged right ventricular cavity, or both.

Vectorcardiographic and Electrocardiographic Analysis

The standard 12 lead electrocardiograms were manually analyzed, using magnifying glasses (×8) for more precise measurements. All the vectorcardiograms (Frank lead system) were automatically analyzed by digital computer. The methods of computer analysis, different in the two centers, have previously been reported.[14–16]

Quantitative analysis: Of the numerous measurements available, some were selected because we thought they might be good indicators of right ventricular hypertrophy in the presence of right bundle branch block. Both magnitude and angular measurements taken from the QRS complex were utilized. Because of the pericardial ST-T changes occurring after surgery, we did not attempt to analyze the repolarization phase.

Measurements of magnitude: *In the standard electrocardiogram,* we analyzed (1) the ratio of the magnitude of the R wave to that of the S wave (R/S ratio) in lead I; (2) the R/S ratio in lead V_6; and (3) the absolute magnitude of R and R′ waves in lead V_1.

In the vectorcardiogram, we used (1) the R/S ratio in lead X; (2) the magnitude of the right maximal spatial vector of the QRS complex; (3) the ratio of the magnitude of the right maximal spatial vector of the QRS complex to that of the left maximal spatial vector; (4) the magnitude of the mean QRS vector in lead X (this value is a time integral obtained by the algebraic integration of all the elementary areas of the QRS complex in lead X; its value is expressed in mv·msec, and a negative value would indicate a net preponderance of the rightward directed forces); and (5) in the Lyon series, the latter measurement was replaced by the relative area of the spatial QRS loop which was oriented to the right (this value was obtained by summing all the elementary octantal areas of the spatial QRS loop that were directed to the right).

Angular measurements: (1) The mean QRS axis in the frontal plane was derived from the standard electrocardiogram by computing Ashman units on the first 0.06 second of the QRS complex. (2) The vectorcardiographic angles were computed by using the formulas reported by Wartak[17]; our reference frame for angular data is shown in Figure 1.

We also analyzed: (1) the angle of the maximal QRS vector in the transverse or horizontal plane; (2) the angle of the maximal QRS vector in the frontal plane; and (3) the azimuth angle of the mean spatial QRS vector. This is the angle between the time integral of the spatial QRS loop area projected onto the horizontal plane and the X axis. This value represents the orientation of a resultant vector, obtained by the summation of all the instantaneous spatial vectors, taking both their magnitude and their time sequence into account. A marked delay of the right potentials, as well as an increased magnitude of the rightward oriented forces, would be responsible for a rightward shift of this vector.

Visual analysis: Visual analysis of the vectorcardiographic loop was performed similarly in the two centers. According to the criteria proposed by Baydar et al.,[6] several morphologic types, based on the configuration of the QRS loop in the horizontal plane, were identified (Fig. 2):

Type I: In this type there is a counterclockwise rotation of the efferent limb of the QRS loop, with a variable rotation of the terminal "appendage." According to the position of the mid temporal portion of the loop as referred to the point of origin (E point), three subtypes were defined: *type* I_p, in which the mid temporal portion of the loop lies posteriorly to the E point; *type* I_o in which the mid temporal portion crosses the E point; and *type* I_A, in which the mid temporal portion is more or less anteriorly displaced.

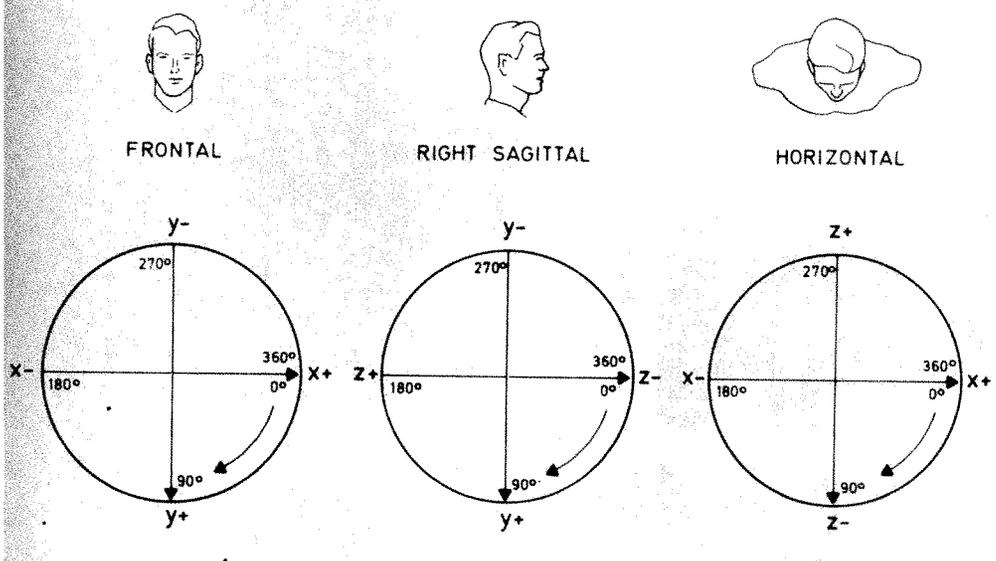


FIGURE 1. Reference frame for angular measurements in electrocardiography.

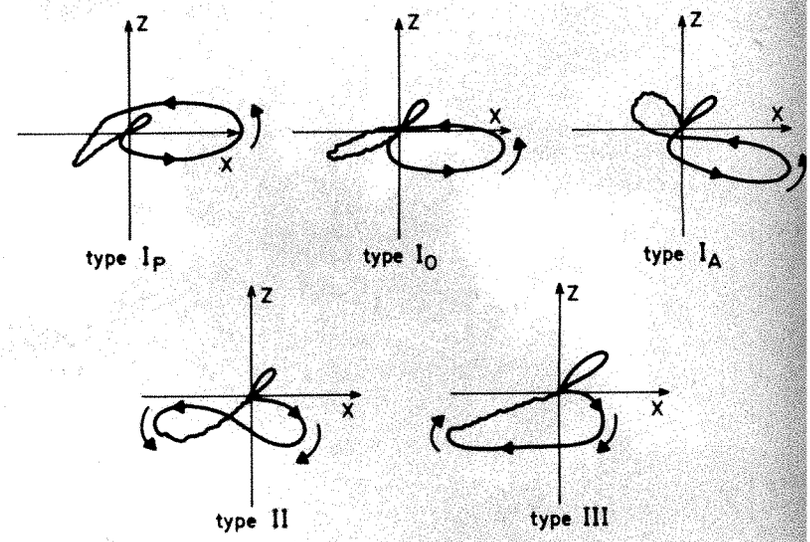


FIGURE 2. Morphologic types of QRS loops in right bundle branch block as projected in the horizontal plane.

Type II: In this type the first half of the QRS loop shows a clockwise rotation with anterior displacement of its mid temporal portion. The terminal appendage is counterclockwise, the entire loop forming a figure eight pattern.

Type III: In this type there is a clockwise rotation of the whole QRS loop, the main electrical forces being oriented anteriorly and to the right. This pattern resembles the so-called "type A" pattern of right ventricular hypertrophy,[18] with the additional finding of a preterminal and terminal slowing of the inscription of the late vectors.

Figure 2 shows that the transition from type I_p to type III is determined by a progressive increase of the anterior displacement of the mid temporal or efferent limb of the QRS loop. This criterion was previously utilized by Fedor et al.[7] in an attempt to quantitate the degree of right ventricular hypertrophy in patients with right bundle branch block.

Statistical study: The statistical significance of the vectorcardiographic differentiation among the clinical groups was analyzed by means of several statistical tests described in the Appendix. For the angular values, the methods of Downs and Liebman[19] were used.

Results

Group Comparisons: Quantitative Analysis

QRS duration: The duration of the QRS complex was not significantly different among the three groups of patients with right bundle branch block. It averaged 127.5 msec in group A (with pure hypertrophy) (range 102 to 164 msec), 127 msec in group B (with mixed hypertrophy) (range 98 to 208 msec) and 125.4 msec in group C (without hypertrophy) (range 92 to 168 msec). With the exception of a few young children, the QRS duration in most cases exceeded the value of 120 msec, which is considered the lower limit for complete bundle branch block in adults.

Magnitude criteria (vectorcardiogram) (Table II): There were few differences between patients in groups A and B. The magnitude of the right maximal spatial vector was slightly greater in group B than in group A. The rather small magnitude of the right maximal spatial vectors in preoperative cases with tetralogy of Fallot has been emphasized by Khoury et al.[20]

In contrast, there were statistically significant differences for all four criteria studied between group C (right bundle branch block without right ventricular hypertrophy) and groups A and B, pooled to form a larger group of patients with right ventricular hypertrophy combined with right bundle branch block. Of particular interest is the much lower value of the R/S amplitude ratio in lead X in group A + B (1.06, versus 3.38 in group C with a much larger variation in the latter group). Also, the magnitude of the right maximal spatial vector and its ratio to the magnitude of the left maximal spatial vector were higher in group A + B. The mean

TABLE II

Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy in the Presence of Right Bundle Branch Block: Magnitude Criteria (mean values ± standard deviation)

Groups	R/S_X	RMSV (mv)	RMSV/ LMSV	$AQRS_X$ (mv·msec)
A (no. = 14)*	1.21 ± 0.80	1.00 ± 0.10	1.27 ± 0.32	−19.94 ± 21.6
B (no. = 24)*	0.98 ± 0.30	1.29 ± 0.24	1.26 ± 0.52	−27.89 ± 14.9
P value	NS	<0.025	NS	NS
C (no. = 14)*	3.38 ± 2.40	0.88 ± 0.09	0.52 ± 0.15	+6.13 ± 12.3
A + B (no. = 38)	1.06 ± 0.47	1.21 ± 0.21	1.26 ± 0.67	−24.96 ± 17.8
P value	<0.0005	<0.005	<0.0005	<0.0005

*For the criteria based on quantitative measurements, only results from the University of Louvain Hospital series are reported.

$AQRS_X$ = magnitude of the mean QRS vector in lead X (time integral [in microvolts × milliseconds]); NS = not significant; *P* = probability; RMSV = magnitude of the right maximal spatial QRS vector (in millivolts); RMSV/LMSV = ratio of the magnitude of the right maximal spatial vector over that of the left maximal spatial vector of the QRS complex; R/S_X = ratio of the magnitude of the R wave to that of the S wave in lead X.

TABLE III

Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy in Presence of Right Bundle Branch Block: Angular Criteria

Groups	Max QRS_{XZ} H°		$\hat{A}QRS_{XZ}$ H°		$\hat{A}QRS_{XYZ}$°
	θ	d	θ	d	(d)
A	104.3	0.60	120°	0.92	
B	120.6°	0.60	120.6°	0.96	
A + B	114.7°	0.60*	120.3°	0.95*	0.90*
C	3.4°	0.96*	58.3°	0.62†	0.54†
A + B versus C	F = 44.4*		F = 26.4*		F = 14.5*

$\hat{A}QRS_{XYZ}$° = angle of the mean spatial QRS vector (its direction in the tridimensional space = spatial analysis); $\hat{A}QRS_{XZ}$ H° = azimuth of the mean spatial QRS vector (angle drawn by the projection of this vector onto the horizontal plane with the X axis-planar analysis); Max QRS_{XZ} H° = angle of the maximal QRS vector in the horizontal plane.

θ = prevalent direction of the vector (see text); d = index of precision for vectorial directions (see text). Statistical significance (see text) for differences in the directions of the vectors between two groups of subjects (F test): P (probability) <0.001 = *, $P<0.01$ = †.

value of $\hat{A}QRS_X$, the time integral of the QRS complex in lead X, was very negative (−24.96 mv·msec) in group A + B, whereas it was slightly positive (+ 6.13 mv·msec) in group C. In the Lyon series, a similar criterion, the relative area of the spatial QRS loop oriented to the right (not shown in Table II), averaged 53.4 percent in group B and only 25.8 percent in group C. This indicates that, in the absence of right ventricular hypertrophy, right bundle branch block cannot by itself produce a sufficient displacement of the mean electrical forces to the right.

Angular measurements (vectorcardiogram) (Table III): The distribution of the vector directions was not significantly different in groups A and B. When these groups were pooled, their vector directions showed significant differences from those of group C. The planar analysis revealed that, in group A + B, the maximal QRS vector angles averaged 114.7° in the horizontal plane, whereas in group C they were closer to the horizontal axis, around 3.4°, with a greater trend to clustering. Similarly, the azimuth angle of the mean spatial QRS vector averaged 120.3° in group A + B but 58.3° in group C, with more clustering in the former.

The spatial analysis was performed by using the spherical coordinates of X, Y and Z leads, according to the formulas described by Downs and Liebman (Table III).[19] Again, a significant difference in the direction of the mean QRS vector between group C and combined group A + B was noted, with more clustering in the latter. This is further illustrated in Figure 3 in which the direction of each individual mean QRS vector in the three groups is projected on the surface of a planisphere. With one exception, all the points from groups A and B are located in the right anterior part of the electrical field (between 90° and 180°), either superiorly or inferiorly. Points from group C are more widely scattered and most are located in the left anterior part (between 0 and 90°) of the electrical field. However, in 4 of the 14 patients without significant right ventricular hypertrophy, the mean spatial QRS vector points to the right.

Electrocardiographic criteria: Table IV shows that a clear differentiation between group C and group

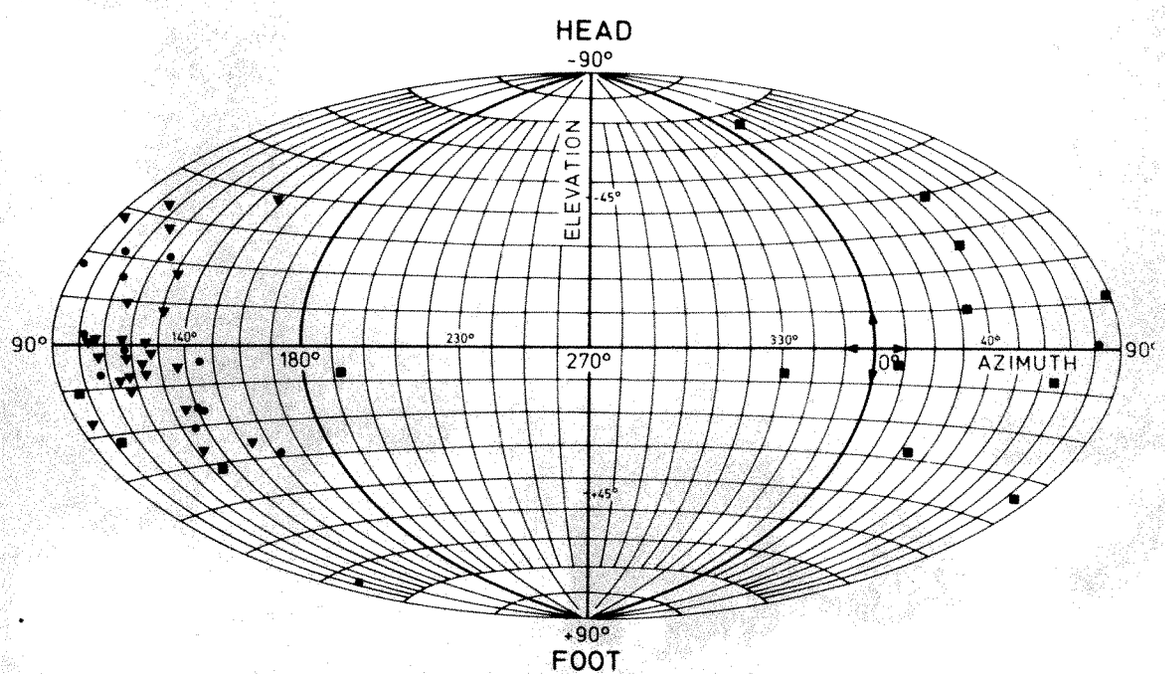


FIGURE 3. Projection of individual mean spatial QRS vectors on a planisphere whose anterior part (0° to 90°) has been unfolded. **Closed circles** = cases in group A (right bundle branch block with "pure" right ventricular hypertrophy); **closed triangles** = cases in group B (right bundle branch block with "mixed" right ventricular hypertrophy); **closed squares** = cases in group C (right bundle branch block without ventricular hypertrophy).

TABLE IV

Diagnosis of Right Ventricular Hypertrophy in the Presence of Right Bundle Branch Block: Electrocardiographic Criteria

Group	R/S_I*	R/S_{V_6}*	R_{V_1}*	R'_{V_1}*	ÂQRS†
C	2.24 ± 1.30	4.44 ± 4.47	3.54 ± 2.16	11.68 ± 5.45	+107.2 ± 62.3
A + B	0.94 ± 0.67	1.66 ± 1.35	4.48 ± 5.75	13.26 ± 10	+136.9 ± 43
P value	<0.0005	<0.005	NS	NS	<0.05

* no. = 69.
† no. = 53; cases with leftward and superior axis deviation (0 → −90°) have been excluded.
ÂQRS = mean QRS axis in the frontal plane (measured from the limb leads) (in degrees); NS = not significant; *P* = probability; R/S_I = R/S ratio in lead I; R/S_{V_6} = R/S ratio in lead V_6; R_{V_1} = magnitude of initial R wave in lead V_1 (in mm or 0.10 mv); R'_{V_1} = magnitude of secondary R wave in lead V_1 (in mm or 0.10 mv).

TABLE V

Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy in Presence of Right Bundle Branch Block: Morphologic Criteria*

Morphologic Types†	Group A + B (no. = 48)	Group C (no. = 24)‡
I_p	15 (31.25%)	18 (75%)
I_O	10 (20.8%)	3 (12.5%)
I_A	15 (31.25%)	3 (12.5%)
II	6 (12.5%)	0
III	2 (4.20%)	0

* Corrected chi square test with 4 degrees of freedom = 13.43 (*P* [probability] <0.01).
† See text for definition.
‡ The visual analysis was performed in both patient series (Louvain and Lyon), except in one patient (group II) for whom no vector loop display was available.

A + B was also possible on the basis of two criteria, namely, the R/S ratios in leads I and V_6 of the electrocardiogram. The values of these ratios were significantly lower in group A + B with right ventricular hypertrophy and right bundle branch block. A third criterion, the mean frontal axis computed from the first 0.06 second of the QRS complex, was also useful in this respect. However, there was no statistically significant difference among the groups with respect to the magnitude of the R wave and that of the R′ wave in lead V_1.

Group Comparisons: Visual Analysis (Vectorcardiogram)

Morphologic types (Table V): There was a statistically significant correlation between the morphologic type of QRS loop and the presence or absence of right ventricular hypertrophy associated with right bundle branch block. Of patients without right ventricular hypertrophy (group C), 75 percent had type I_p, 25 percent type I_o or I_A and no patient had type II or type III. Of patients with right ventricular hypertrophy (group A + B), 16.7 percent had type II or III, 31.2 percent had type I_A and 52 percent had type I_o or I_p.

Table VI presents the same data in another way. In group C, of 24 cases without right ventricular hypertrophy, only 3 (12.5 percent) showed some anterior displacement of the mid portion of the QRS loop (type I_A, II or III). In group A + B, there was an almost equal distribution among types I_p and I_o (25 of 48 = 52 percent) and types I_A, II and III (23 of 48 = 48 percent).

Role of left fascicular block: Another possible cause for anterior displacement of the QRS loop in right bundle branch block is the addition of left fascicular block, which can also be produced by the surgical repair of a ventricular septal defect. However, in this series, this association did not seem to affect the morphologic pattern in the horizontal plane: Of the 73 subjects, 10 had left anterior fascicular block associated with right bundle branch block. In 6 of these 10 subjects (3 from group C, 2 from group B and 1 from group A) there was a type I_p pattern; 2 subjects (both in group B) had a type I_o and I_A pattern, respectively; the remaining 2 (both in group B) had a type II and type III pattern, respectively, but in these the morphologic type was probably related more to the right ventricular hypertrophy than to the left fascicular block.

TABLE VI

Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy in Presence of Right Bundle Branch Block: Morphologic Criteria

Group	Morphologic Types $I_p + I_O$	Morphologic Types $I_A + II + III$
A + B (no. = 48)	25	23
C (no. = 24)	21	3

* Corrected chi-square test with 1 degree of freedom = 7.23 (*P* [probability] <0.01).

Correlation of Postoperative Vectorcardiogram and Hemodynamic Status

We have investigated the correlation between the vectorcardiographic criteria of right ventricular hypertrophy in these patients with postsurgical right bundle branch block and the residual right ventricular overload assessed from the postoperative measurement of right ventricular systolic and mean pulmonary arterial pressures. Only subjects whose vectorcardiographic and hemodynamic studies had been performed within the same week were selected for this part of the study. In the 17 patients with tetralogy of Fallot, there was no significant correlation between the vectorcardiographic measurements and the level of systolic right ventricular pressure. In the 10 patients operated on for a ventricular septal defect with pulmonary hypertension, some vectorcardiographic criteria of right ventricular hypertrophy were more closely related to the hemodynamic indicators of a residual right ventricular overload: These were the mean QRS vector in lead X versus right ventricular systolic pressure ($r = -0.73$, $P < 0.001$) and versus mean pulmonary arterial pressure ($r = -0.64$, $P < 0.001$), and the right maximal spatial vector versus mean pulmonary arterial pressure ($r = 0.57$, $P < 0.001$).

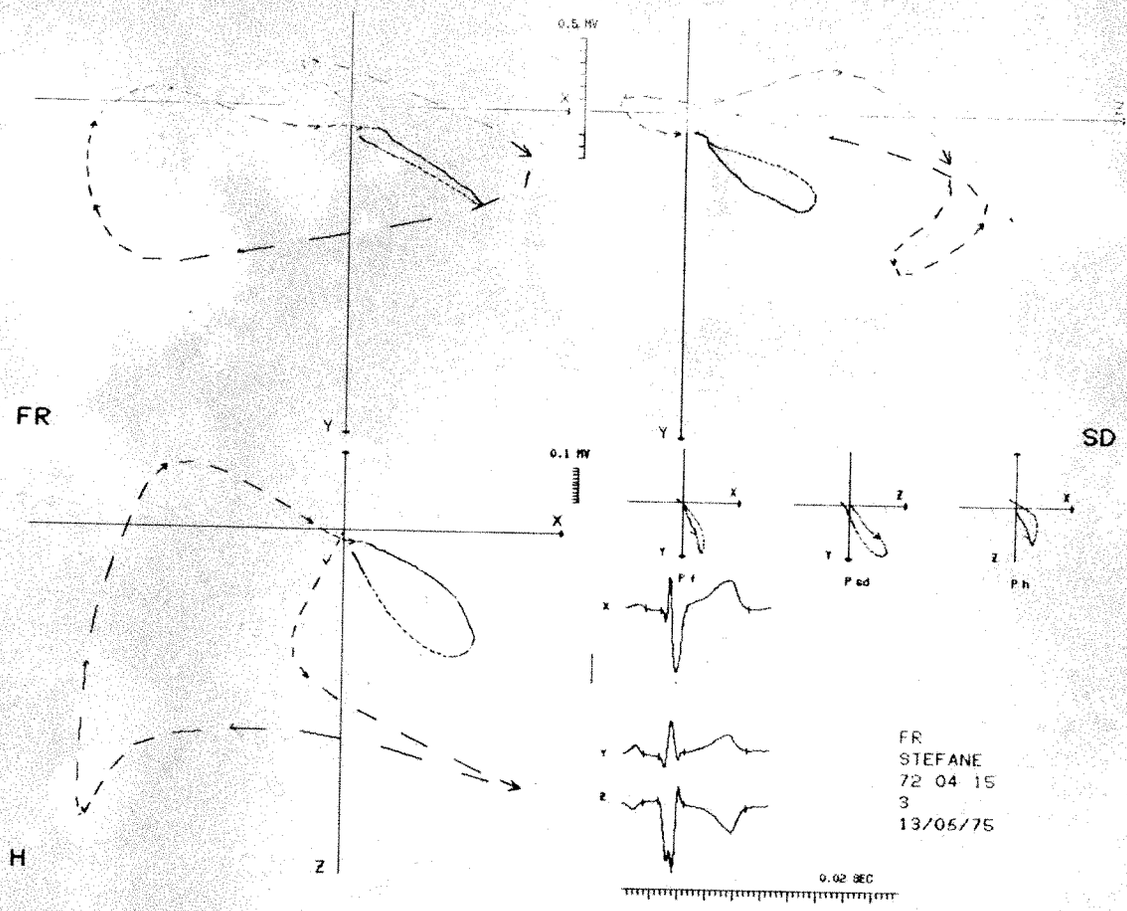


FIGURE 4. Preoperative vectorcardiogram of a 3 year old child with tetralogy of Fallot. The P loop is separated from the QRS-T loops (Pf, Psd and Ph). On the QRS loop, the dashes are 2 msec apart from each other; each **small arrow** represents a 10 msec vector and the **larger arrow** the initial 30 msec vector. The X, Y and Z leads are also shown. This tracing shows a "type A" right ventricular hypertrophy: marked right axis deviation in the frontal plane and clockwise rotation and anterior displacement of the main QRS forces in the horizontal plane. QRS duration = 90 msec. FR = frontal plane; H = horizontal plane; SD = right sagittal plane.

TABLE VII

Detection of Right Ventricular Hypertrophy in Individual Cases With Right Bundle Branch Block: Vectorcardiographic Criteria

Criteria	Sensitivity* (%)	Specificity† (%)
$R/S_X < 2.0$	89.5	100
$\hat{A}QRS_X < -10$ mv-msec	81.5	92.8
Relative area to the right ≥40 percent	83.3	88
$\hat{A}QRS_{XYZ}$ H° between 90° and 180°	97	75
Max QRS_{XZ} H° between 90° and 270°	73	100
Max QRS_{XY} F° between 90° and 270°	50	100

$\hat{A}QRS_X$ = mean QRS vector in lead X; $\hat{A}QRS_{XYZ}$ H° = azimuth angle of the mean spatial QRS vector; Max QRS_{XY} F° = angle of maximal QRS vector in frontal plane; Max QRS_{XZ} H° = angle of maximal QRS vector in horizontal plane; R/S_X = R/S wave magnitude ratio in lead X.

* Sensitivity = number of cases correctly diagnosed as right ventricular hypertrophy by the vectorcardiogram over the total number of cases with a true right ventricular overload as confirmed by independent criteria.

† Specificity = number of cases correctly diagnosed as isolated right bundle branch block, without right ventricular hypertrophy, by the vectorcardiogram, over the total number of cases in which no right ventricular overload was found on the basis of independent criteria.

Detection of Right Ventricular Hypertrophy in Individual Subjects With Right Bundle Branch Block

The vectorcardiographic classification in various morphologic types did not allow a good discrimination between the presence and absence of right ventricular hypertrophy in *individual subjects* with right bundle branch block (Table V). The great variability of the morphologic patterns was further demonstrated by the

TABLE VIII

Detection of Right Ventricular Hypertrophy in Individual Cases With Right Bundle Branch Block: Electrocardiographic Criteria

Criteria	Sensitivity* (%)	Specificity* (%)
$R/S_I < 1.0$	66	86.3
$R/S_{V_6} < 1.6$	63.8	86.4
$\hat{A}QRS$ between 90° and 270°	90.5	63.6

* Defined as in Table VII.

$\hat{A}QRS$ = mean QRS axis in the frontal plane; R/S_I = R/S wave magnitude ratio in lead I. R/S_{V_6} = R/S wave magnitude ratio in lead V_6.

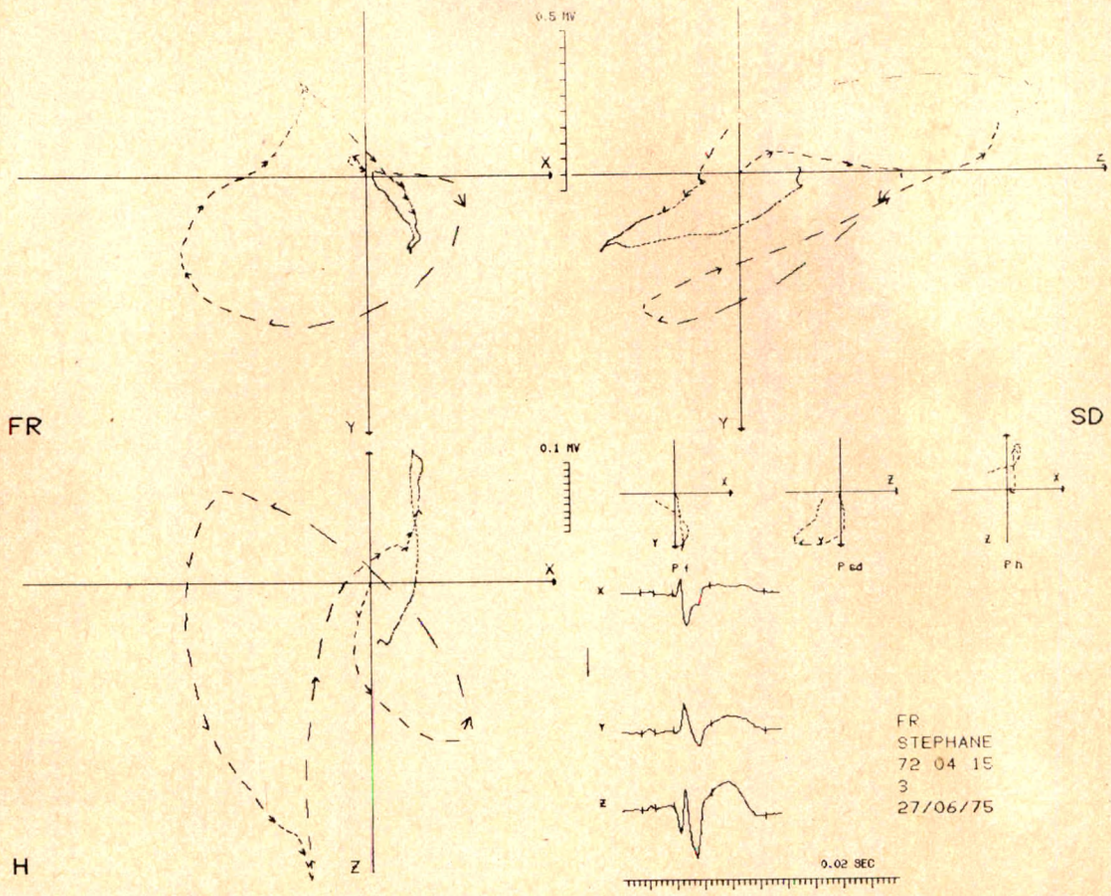


FIGURE 5. Same patient. Postoperative vectorcardiogram (8 days after complete surgical correction). There is now a type I_0 pattern of right bundle branch block (QRS duration = 118 msec). The maximal QRS vector remains oriented to the right in the frontal plane. The superior displacement of the terminal vectors in that plane could be related to the large resection of the crista supraventricularis which had to be performed. The large area of the QRS loop oriented anteriorly and to the right suggests right ventricular hypertrophy superimposed on the right bundle branch block.

lack of correlation between the QRS configuration before and after operation. Right ventricular hypertrophy of "type A" [18] did not necessarily correspond to type II or type III in the postoperative period (Fig. 4 and 5).

The addition of quantitative criteria enhanced the performance of the diagnostic classification in individual patients with right bundle branch block. Tables VII and VIII present, respectively, the sensitivity and specificity values of the vectorcardiogram and the electrocardiogram in detecting right ventricular hypertrophy associated with right bundle branch block.

Vectorcardiogram (Table VII): The best values for specificity were obtained with (1) an R/S ratio in lead X of less than 2.0, and a maximal QRS vector oriented to the right in the frontal (2) and horizontal (3) planes. These criteria also had a high sensitivity level, except for the criterion based on the direction of the maximal QRS vector in the frontal plane. For example, with this value between 90° and 270°, there were no false positive findings but 50 percent of the patients with true right ventricular hypertrophy did not meet this criterion. The best compromise between a high sensitivity and a high specificity level was obtained by using the criterion of an R/S ratio of less than 2.0, followed by a more negative value than −10 mv·msec for the mean QRS vector in lead X. Because of the high levels of sensitivity and specificity obtained with use of a single criterion, no further attempt was made to perform a multivariate analysis of the same data.

Electrocardiogram (Table VIII): Both the sensitivity and specificity values were lower for the electrocardiographic than for the vectorcardiographic criteria. With a 9 percent false positive rate, the sensitivity level was well below 70 percent for the two criteria based on the R/S ratio in leads I and V_6. Only a mean QRS axis of more than +90° reached a sensitivity level of 90 percent.

Discussion

Diagnostic value of electrocardiogram: It is generally recognized that the electrocardiographic diagnosis of right ventricular hypertrophy in the presence of complete right bundle branch block is difficult.[1,2] The criteria proposed by Barker,[21] based on the height of the R′ wave in lead V_1, are not reliable because they result in many false positive and false negative findings.[3] In an autopsy series, Booth et al.[22] were unable to relate the height of the R′ wave in the right precordial leads

to a right or left ventricular preponderance. Another criterion, the rightward shift to more than +90° or even +110° of the mean QRS axis computed from the first 0.06 second of the QRS complex, can be fulfilled in many other conditions[23]; however, these conditions are less frequent in a pediatric population than among adults.

In our study, neither the magnitude of the R′ wave nor that of the primary R wave in lead V_1 was a good discriminator for the association of right ventricular hypertrophy and right bundle branch block. An R′ wave in lead V_1 of 15 mm or greater was found in only 14 of 46 subjects with right ventricular hypertrophy but also in 7 of the 22 without ventricular hypertrophy (false negative rate 68 percent, false positive rate 33 percent). The mean QRS axis in the frontal plane was a good criterion for group differentiation: it averaged 136.9° in the group with right ventricular hypertrophy but only 103.2 in the group without right ventricular hypertrophy. The criterion based on a mean QRS axis superior to +90° performed the best for the individual detection of right ventricular hypertrophy, giving a 9.5 percent false positive and a 36.3 percent false negative rate. Other good electrocardiographic criteria for group differentiation were the R/S ratios in leads I and V_6; their mean values were significantly different in the two groups. However, the vectorcardiographic criteria were generally better in detecting right ventricular hypertrophy in individual subjects with right bundle branch block.

Diagnostic value of vectorcardiogram: The diagnostic value of the vectorcardiogram in detecting right ventricular hypertrophy in the presence of right bundle branch block remains controversial.[6,7,11,24–26] Some authors have used the vectorcardiogram to differentiate between cases of isolated right bundle branch block and cases with associated right ventricular overload, usually resulting from heart or lung disease. According to Fedor et al.,[7] the anterior displacement of the mid temporal limb of the QRS loop in the horizontal plane might be an early indicator of right ventricular hypertrophy in such patients. The clockwise rotation of the efferent limb of the QRS loop in the horizontal plane was the best criterion for the diagnosis of right ventricular hypertrophy associated with right bundle branch block.[6,7] However, in a recent report, Tokunaga[11] showed that a clockwise rotation of the QRS loop in the horizontal plane can be present in cases of isolated right bundle branch block; in experimental studies he also demonstrated the great variability of the morphologic patterns of right bundle branch block.[27] By initiating atrial premature beats through a transvenous catheter electrode to produce aberrant ventricular conduction, Cohen et al.[28] were able to reproduce various patterns of right bundle branch block, some of them with clockwise rotation of the transverse QRS loop. In an adult population, several other factors, such as a true posterior myocardial infarction or a left anterior or left posterior fascicular block, which can also modify the pattern of right bundle branch block, must be taken into account.[8,9,23] More recently,[10,29] it has been shown that a lesion of the mid septal fibers of the left bundle could also produce an anterior displacement with clockwise rotation of the QRS loop; when associated with a right bundle branch block, this particular variety of bifascicular block would then reproduce a type II or III pattern of QRS vector loop.

Our study has clearly demonstrated the value of quantitative analysis of the vectorcardiogram in diagnosing right ventricular hypertrophy combined with right bundle branch block. The two groups of patients with right bundle branch block, those with and those without right ventricular hypertrophy, were easily separated on the basis of a few criteria. The ratio between the magnitude of the R wave and that of the S wave (R/S ratio) in lead X, a value easily computed by hand, was very useful in this respect. Less reliable was the angle of the maximal QRS vector in the frontal plane; about half of the patients with right ventricular hypertrophy had no rightward displacement of this vector. The angle drawn by the maximal QRS vector in the horizontal plane was a much better discriminator.

More sophisticated measurements yielded other valuable criteria. These were the magnitude of the right maximal spatial vector, its ratio to the amplitude of the left maximal spatial vector, the value of the mean QRS vector in lead X, the azimuth angle of the mean spatial QRS vector and the relative area of the spatial QRS loop developed in the right part of the electrical field. The latter three criteria correspond to the rightward shift of the time integral of the QRS loop. These measurements represent the net effect of combined right ventricular hypertrophy and right bundle branch block on the successive instantaneous QRS vectors, including their magnitude and time course. This result could be expected from the electrophysiologic properties of the association: The right ventricular hypertrophy already contributes to the increased voltages to the right; the right bundle branch block is responsible for the delayed right ventricular depolarization, leading to a displacement to the right of the mid and late portions of the QRS loop. The combination of these two factors has a cumulative affect on the spatial QRS loop, producing a larger area oriented to the right than occurs with either right ventricular hypertrophy or right bundle branch block alone.

Value of QRS loop morphologic criteria: The morphologic criteria were less able to differentiate between the two groups of patients. Types II and III, showing an anterior displacement with clockwise rotation of the efferent limb of the QRS loop in the transverse plane, do indicate the association of right ventricular hypertrophy with right bundle branch block. However, like Baydar et al.,[6] we found that this criterion is not very sensitive: In our series more than 80 percent of the patients with proved right ventricular hypertrophy showed the more classic pattern of right bundle branch block, represented by Types I_p, I_o or I_A. The rather high proportion of types I_p and I_o in this series of mainly young children was surprising. In children, because the efferent limb of the QRS loop is normally more anterior than in older subjects, one would have

expected more instances of types I_A, II or III because of the additional effects of the right ventricular hypertrophy and right bundle branch block in these young patients. In fact, the morphologic patterns showed a greater variability, as demonstrated by the changes in the postoperative records. The right ventricular conduction defect can considerably modify the preexisting configuration of the QRS loop. In patients operated on for tetralogy of Fallot, there was a rapid transition from a "type A" right ventricular hypertrophy toward a type I bundle branch block (Fig. 4 and 5) a few weeks after the surgical procedure. This finding could perhaps be explained by the dramatic improvement in pulmonary blood flow leading to a sudden decrease in right ventricular pressure, by a decrease in right ventricular stroke volume and also by the large excision of right ventricular muscle. By comparison, there were proportionally more cases of right bundle branch block with a type II and III pattern in patients operated on for a ventricular septal defect; in these patients the pulmonary hypertension probably decreased more slowly and some degree of right ventricular hypertrophy might have persisted for longer periods.

Factors influencing electrocardiographic analysis in individual patients: It is tempting to rely on the vectorcardiogram to diagnose the presence or absence of concomitant right ventricular hypertrophy in individual patients with right bundle branch block. However, several factors must be considered in relation to this vectorcardiographic diagnosis. First, in a correlation of the postoperative vectorcardiographic and hemodynamic measurements, the vectorcardiogram did not allow an accurate prediction of the level of pulmonary or right ventricular pressure. A significant correlation was found only for patients operated on for a ventricular septal defect, a finding that could, again, be related to the more progressive improvement of their postoperative hemodynamic status together with the preservation of the anatomic integrity of the cardiac structures. Second, one must consider the group being examined. The vast majority of our patients were children. The mean age was slightly higher in those without right ventricular hypertrophy (group C), but the difference was probably too slight to influence the results. In children, other conditions that might result in a pattern similar to types II and III right bundle branch block, such as true posterior myocardial infarction and left fascicular block, are much rarer than in older patients, and thus the differential diagnosis is simpler in the pediatric age group. Third, in most subjects with associated right ventricular hypertrophy (groups A and B) right bundle branch block was surgically induced, whereas in more than half of the patients in group C the block was of nonsurgical origin.

One might consider whether the location of the right ventricular conduction defect could have accounted for some of the changes attributed to the right ventricular hypertrophy. The right bundle branch block produced by surgery can have various origins: a central lesion of the proximal right bundle at the time of closure of the septal defect,[30] a peripheral lesion due to disruption of the Purkinje network during the right ventriculotomy[31,32] and the resection of the conus pulmonaris (crista supraventricularis).[20,26] In our series, a preliminary study[13] showed that the exact site of the conduction defect could not be definitely ascertained. We found great variability in the direction of the initial forces of the QRS loop with no specific pattern of the main QRS loop. Our subjects with surgically induced block did not necessarily display a greatly distorted QRS loop, as previously suggested by de Lezo et al.,[33] but in some of our patients with tetralogy of Fallot the superiorly and rightward oriented terminal vectors could be related to the extensive excision of the crista supraventricularis as a result of very tight infundibular stenosis with hypertrophy of the outflow tract of the right ventricle. On the other hand, a peripheral type of right bundle branch block, such as that caused by the ventriculotomy, should induce a lesser degree of rightward and anterior displacement of the late QRS forces. Indeed, the incomplete disruption of the Purkinje network would result in a rightward terminal delay with some portions of the right ventricular mass still being depolarized earlier than they would be in the presence of a proximal and total block. Therefore, we believe that the modifications in the QRS vectorcardiogram of our patients were mainly caused by the right ventricular hypertrophy and were not related to the mode of production or the site of the bundle branch block.

Implications: In our special patient population—that is, young patients with surgically induced right bundle branch block—the presence of a concomitant right ventricular hypertrophy was suggested by any one of the following vectorcardiographic criteria: (1) a clockwise rotation of the QRS loop in the horizontal plane; (2) an R/S ratio *of the R over S wave* in lead X of less than 2.0; (3) a maximal QRS vector in the horizontal plane located between 90° and 270°; or (4) a mean QRS vector in lead X more negative than −10 mv·msec. In contrast, if the R/S ratio in lead X is equal or superior to 2 or if the azimuth angle of the mean spatial QRS vector is not between 90° and 180°, right ventricular hypertrophy was only a remote possibility. These criteria will have to be validated in a different series of similar patients. Their validity should also be established by following up the reduction in signs of right ventricular overload in longitudinal studies of the same patients several years postoperatively.

APPENDIX

Statistical Tests Used to Evaluate Differences In Vectorcardiographic Criteria Among Clinical Groups

1. The differences in the distributions of the morphologic types were evaluated with a chi-square test, using the Yates correction for discrete variables.

2. The differences in the magnitude criteria were evaluated using Student's t test for unpaired data.

3. The differences in the vectorcardiographic angular measurements were evaluated with the "the center of gravity"

method, where θ represents the "*prevalent direction*" of the vectors represented as points in a plane or on the surface of a sphere and d is an "*index of precision*" indicating a trend toward the clustering of the points on the edge of a disk (planar analysis) or in the region of the surface of the sphere (spatial analysis). d represents the distance from the center of the disc or of the sphere to the center of gravity of the points; its value ranges from 0 to 1: The greater the clustering of the points, the greater the distance to their center of gravity. The value of d, together with N, the number of observations, or the sample size, is used in a chi square test to verify the statistical significance of the preferential distribution of the points. The difference in the angular directions between two populations can be assessed by using an F test with 1 and N-1 degrees of freedom in the planar analysis and 2 and 2N-4 degrees of freedom in the spatial analysis. Down and Liebman[19] have provided more details about these methods of statistical treatment of angular values in vectorcardiography.

4. For the mean frontal plane QRS axis derived from the standard electrocardiogram, after cases of left axis deviation (0 to −90°) were excluded, only positive values (0 to +90° to +180° to +270°) were considered and an unpaired t test was used.

Acknowledgment

We are indebted to Isabella Moschion for secretarial assistance and we thank H. Kulbertus, MD and J. M. Detry, MD for review of the manuscript.

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Maximal Exercise Capacity of Children With Heart Defects

GORDON R. CUMMING, MD, FRCP(C), FACC

Winnipeg, Manitoba, Canada

Maximal treadmill tests following the Bruce protocol were performed by 830 children with heart defects and the endurance times compared with normal values from 327 children seen in the same clinic because of normal murmurs and from 388 normal children randomly selected and tested in the schools. When values in the normal clinic children were used as the reference, only 21 percent of the patients with heart defects had endurance times below the 10th percentile line. This line was 14 percent higher in the normal school children, and 47 percent of the patient group had values below the 10th percentile when values in the school children were used as the reference. Maximal heart rate in children with heart defects was almost always in the normal range (180 to 210 beats/min) except in patients with cyanosis or severe valve disease and, when encouraged to continue exercising, even these children had a mean maximal heart rate of 175 beats/min. When comparing the exercise capacity of children with heart defects with that of normal children, the source of the normal children is important; body build needs to be considered, as well as physical activity habits. Clinic patients without heart defects probably serve as a better normal control group than children obtained from the school system. Maximal exercise tests do not necessarily distinguish between children with mild or severe heart disease. Only children with lesions causing cyanosis or children with obviously severe disease have consistent reductions in exercise capacity.

There is some controversy over the frequency of impaired exercise capacity in children with heart defects. Goldberg et al.[1,2] reported that at least 80 percent of children with cardiac defects had a lower exercise capacity than that of normal children when tested with a progressive bicycle exercise test. This information contradicts that found by questioning parents of children attending cardiac clinics and that reported by Kramer and Lurie[3] in 1962 and by this laboratory[4] in 1974 in studies using maximal bicycle exercise. To assess the frequency of impaired exercise capacity in children with heart defects, we reviewed 830 consecutive maximal treadmill exercise tests performed by children with heart defects and compared the results with those of children attending the same clinics who were found to have a normal heart. An additional comparison was made between the children with heart defects and a second series of normal children from the school system.

Material and Methods

Subjects

Patients aged 5 or more years attending an outpatient cardiac clinic and a hospital-based office practice of pediatric cardiology over a 3 year period were routinely sent to the exercise laboratory for maximal treadmill exercise testing. About half the 4 year olds seen during this time were also tested when clinical judgment suggested that adequate cooperation would be obtained. The exercise test was used as a routine part of the patient's cardiac evaluation in the same manner as an electrocardiogram. The 830 patients tested were representative of those with heart defects in the community at large because this center not only is a major referral center with a concentration of serious medical problems, but also serves the majority of the specialty pediatric needs for an urban population

From the Department of Pediatrics, Health Sciences Children's Centre and the University of Manitoba, Winnipeg, Manitoba, Canada. Financial support was received from the Children's Hospital of Winnipeg Research Foundation, Winnipeg, Manitoba, Canada. Manuscript received February 21, 1978; revised manuscript received May 23, 1978, accepted May 24, 1978.

Address for reprints: G. R. Cumming, MD, Children's Centre, 685 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E 0W1.

TABLE I

Age Distribution of Subjects

Age Group (yr)	Subjects (no.) Patients With Heart Defects	Normal Clinic Group	Normal School Group
4–5	118	76	0
6–7	121	62	56
8–9	123	56	62
10–12	181	59	88
13–15	134	50	94
16+	153	24	88
Totals	830	327	388

of a half million persons and another half million persons dispersed over 250,000 square miles.

Some patients were not tested because of significant infection, orthopedic problems or severe mental retardation or because the exercise equipment or technicians, or both, were not available, but more than 90 percent of the patients seen over the 3 year period were tested. The tests were carried out when the subjects visited the clinic with no standardization of time of day, meals, clothing or other factors. No patient had clinical evidence of heart failure at the time of testing.

The 715 normal children studied comprised two groups: 327 children previously reported on[5] who were tested in the same clinic as the patient group and found to have an innocent murmur and 388 volunteers aged 6 to 18 years from two schools who were tested on the same treadmill used by the patient group. The former normal subjects will be referred to as the normal clinic group, the latter as the normal school group. Patients in the school group were obtained toward the end of this study; the children were selected randomly from those who had returned parental consent forms. Children aged 4 and 5 years were not tested in the schools. The number of subjects by age in the abnormal and two normal groups is listed in Table I.

The condition of the children with heart defects was arbitrarily classified as mild, moderate or severe on the basis of the cardiac catheterization data listed in Table II. A single postoperative classification was used regardless of the completeness of repair of the defect. The number of subjects with both pre- and postoperative exercise studies is not sufficiently large at this time to present a detailed analysis, and the time interval between operation and testing (6 months to 10 years) was not taken into consideration. Several patients with a small ventricular septal defect and mild aortic or pulmonary stenosis by clinical criteria did not have catheterization studies and their condition was classified as mild. Rheumatic heart disease was classified as mild if cardiac enlargement clinically and radiologically was absent or borderline, and severe if marked

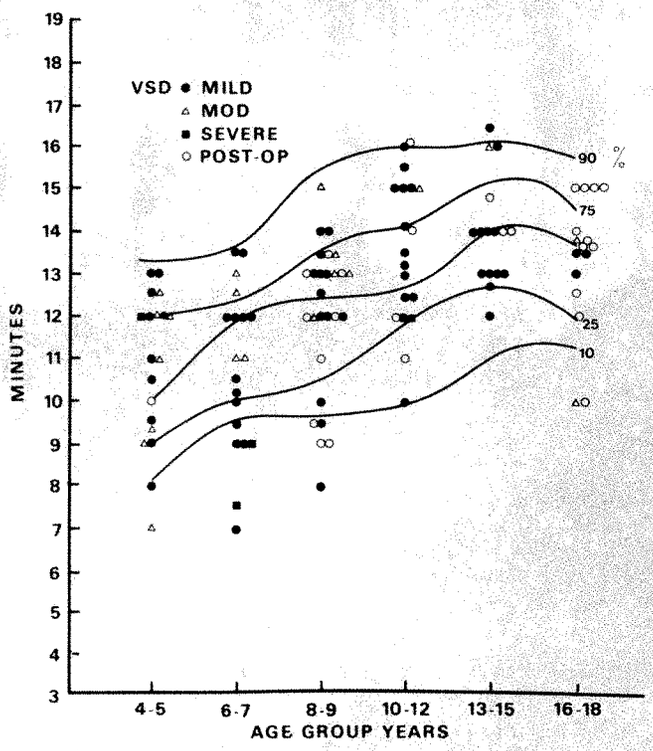


FIGURE 1. Endurance times for patients with ventricular septal defect (VSD) of different severity, plotted against percentile values for patients without heart disease seen in the cardiac clinic. Percentile values are given at right. MOD = moderate; POST-OP = postoperative.

cardiac enlargement was present, accompanied by loud murmurs of mitral or aortic regurgitation, or both.

Exercise

The Bruce treadmill protocol was followed. Its use in clinic children without cardiac defects has been described.[5] No hanging on or touching of the guard rails was allowed, and all children, regardless of cardiac diagnosis, were given considerable verbal encouragement to continue exercising as long as possible. It was not necessary to stop the exercise test in any child because of arrhythmia or chest pain and, although exercise S-T changes were monitored, S-T depression was not used as an indication for stopping a test. The end point of the test occurred when the children could not or would not exercise any longer and clung to the guard rails refusing to let go, jumped off the treadmill or hung onto the observer stationed at their side or behind them. Heart rate was obtained from electrocardiographic lead CM_5. The tests of nine children (1 percent) were discarded because the observer believed that

TABLE II

Grading of Severity of Heart Defects

Severity	Atrial Septal Defect	Ventricular Septal Defect	Aortic Stenosis	Pulmonary Stenosis
Mild	$\dot{Q}p/\dot{Q}s \leq 1.5$ and PA systolic pressure <30 mm Hg	$\dot{Q}p/\dot{Q}s \leq 1.3$ and PA systolic pressure <30 mm Hg	Peak gradient ≤30 mm Hg	Peak gradient ≤30 mm Hg
Moderate	$\dot{Q}p/\dot{Q}s$ 1.6–2.5 and PA systolic pressure ≤50	$\dot{Q}p/\dot{Q}s$ 1.4–2.0 or PA systolic pressure <50, or both	Gradient 31–45	Gradient 31–55
Severe	$\dot{Q}p/\dot{Q}s$ >2.5 or PA systolic pressure >50	$\dot{Q}p/\dot{Q}s$ >2.0 or PA systolic pressure >50 or history of pulmonary banding	Gradient >45	Gradient >55

PA = pulmonary artery; $\dot{Q}p/\dot{Q}s$ = pulmonary/systemic flow ratio.

a reasonable maximal effort was not made. These children were either 4 or 5 years old or teenage girls. Five technicians took part in the collection of the data, working in pairs until experience was gained, and one of these technicians took part in the collection of normal data in the schools. The same treadmill and electrocardiogram were used for the patient and normal school groups.

Results

Comparison of patients with heart defects and normal clinic group: The endurance times of the patients with heart defects were plotted on percentile charts constructed from the tests on patients without defects (Fig. 1). From these charts data were prepared in tabular form (Tables III and IV). Results for the entire series in comparison with those of the normal clinic group are shown in Table III. The mean age of the patients was 10 years, and the mean maximal heart rate 198 beats/min. The maximal heart rate was 180 beats/min or greater in 738 tests (89 percent), and when patients with cyanotic disease were excluded, a maximal heart rate of less than 180 beats/min occurred in only 3 percent of the tests. The percent of subjects of each diagnostic category in selected percentile ranges for endurance times is also given in Table III. We arbitrarily selected the 10th percentile line as the lower limit because of the relatively small number of subjects in the normal series and a conviction that patients with lower values have suboptimal levels of fitness.

In comparison with the normal clinic group, a greater than expected number of exercise capacity values were below the 10th percentile category for children with a moderate or severe ventricular septal defect, severe atrial septal defect, severe and postoperative aortic stenosis, moderate and postoperative pulmonary stenosis, tetralogy of Fallot before or after surgery, other cyanotic lesions, postoperative coarctation of the aorta or severe rheumatic heart disease. However, many children in these classifications also had an exercise capacity above the 50th percentile level, including patients with a moderate ventricular septal defect (59 percent), severe ventricular septal defect (19 percent), severe atrial septal defect (11 percent), severe aortic stenosis (35 percent), postoperative aortic stenosis (19 percent), moderate pulmonary stenosis (51 percent), postoperative pulmonary stenosis (20 percent) and postoperative tetralogy of Fallot (22 percent). With the exception of three groups—patients with mild aortic stenosis, moderate pulmonary stenosis and rheumatic

TABLE III

Endurance Times on Bruce Treadmill Test: Patients With Heart Defects versus Normal Clinic Subjects, Aged 4 to 20 Years

Defect	Cases (no.)	Age (yr) (mean ±SD)	Maximal HR (beats/min) (mean ±SD)	HR <180 (no.)	Percentile Ranges of Normal Clinic Group (percent of patients) 10th	11th to 25th	26th to 50th	51st to 70th	76th to 90th	>90th
VSD										
Mild	123	10 ± 4	204 ± 10	2	6	16	27	30	18	4
Moderate	39	8 ± 4	202 ± 10	3	18	5	18	41	15	3
Severe	21	8 ± 3	196 ± 7	3	29	29	24	14	0	5
Postop	44	12 ± 4	197 ± 8	2	9	14	30	32	13	2
ASD										
Mild	27	10 ± 4	201 ± 9	0	11	4	30	30	19	7
Moderate	37	10 ± 4	200 ± 7	0	3	16	19	32	22	8
Severe	9	5 ± 2	200 ± 7	0	33	11	44	11	0	0
Postop	43	13 ± 6	198 ± 8	1	9	14	35	26	12	5
PDA										
Postop	10	12 ± 7	200 ± 10	1	0	10	40	50	0	0
AS										
Mild	51	10 ± 3	203 ± 8	0	0	24	24	22	18	14
Moderate	20	9 ± 3	207 ± 6	0	0	15	30	40	15	0
Severe	14	7 ± 1	198 ± 7	0	14	7	43	21	14	0
Postop	27	12 ± 3	198 ± 9	1	22	19	41	15	4	0
PS										
Mild	61	11 ± 4	200 ± 7	2	11	16	36	31	3	
Moderate	16	8 ± 3	206 ± 9	0	19	31	0	38	0	13
Severe	5	9 ± 4	198 ± 8	0	0	40	40	20	0	0
Postop	15	12 ± 4	197 ± 9	1	20	40	20	20	0	0
Coarct										
Preop	24	7 ± 4	197 ± 7	0	13	20	17	33	13	4
Postop	23	12 ± 4	204 ± 8	0	22	17	43	13	4	0
T of F										
No op	12	6 ± 3	178 ± 8	10	67	25	8	0	0	0
Post shunt	10	6 ± 3	192 ± 7	1	90	0	10	0	0	0
Post-open heart surgery	37	12 ± 4	188 ± 11	5	19	19	41	11	11	0
Other cyanotic*	71	10 ± 4	175 ± 14	53	92	4	3	0	0	0
Rheumatic fever										
Normal heart	25	11 ± 3	204 ± 9	0	8	16	24	20	28	4
Mild-moderate valve	51	13 ± 4	199 ± 10	3	12	12	22	24	18	14
Severe valve disease	15	12 ± 3	181 ± 4	4	47	20	33	0	0	0
Total or mean	830	10 ± 3	198 ± 8	92	21%	15%	25%	23%	11%	4%

* Other congenital lesions associated with cyanosis.

AS = aortic stenosis; ASD = atrial septal defect (secundum); Coarct = coarctation of aorta; HR = heart rate; OP = operation; PDA = patent ductus arteriosus; postop = postoperative; preop = preoperative; PS = pulmonary stenosis; SD = standard deviation; T of F = tetralogy of Fallot; VSD = ventricular septal defect.

TABLE IV

Cardiac Patient versus Normal Values Obtained in the Schools—Subjects Aged 6 to 20 Years

Defect	no. of Subjects	Percentile Ranges of Normal School Group (percent of patients) ≤10th	11th to 25th	26th to 50th	51st to 75th	76th to 90th	>90th
VSD							
Mild	98	33	9	16	12	12	7
Moderate	27	22	19	37	7	11	4
Severe	16	81	0	6	6	0	6
Postop	44	32	20	23	16	9	0
ASD							
Mild	27	22	22	22	0	11	11
Moderate	30	27	27	20	7	10	10
Severe	7	43	43	14	0	0	0
Postop	39	44	21	15	27	13	5
PDA							
Postop	8	13	38	13	25	13	0
AS							
Mild	40	23	18	30	13	8	10
Moderate	19	32	32	11	16	5	5
Severe	13	31	38	0	31	0	0
Postop	27	74	7	11	4	4	0
PS							
Mild	51	43	16	24	10	6	2
Moderate	12	42	0	33	17	0	8
Severe	5	40	40	0	20	0	0
Postop	15	73	7	7	13	0	0
Coarct							
Preop	12	42	25	8	16	8	0
Postop	22	64	23	14	0	0	0
T of F							
No op	7	86	14	0	0	0	0
Post-shunt	5	100	0	0	0	0	0
Post-open heart	37	54	24	11	3	5	5
Other cyanotic	62	100	0	0	0	0	0
Rheumatic fever							
Normal heart	24	38	4	7	21	8	13
Mild-moderate valve disease	50	38	6	20	16	8	12
Severe valve disease	15	93	0	7	0	0	0

Abbreviations as in Table III.

TABLE V

Endurance Times of 712 Patients With Heart Defects Aged 6 to 20 Years: Comparison of Overall Results Using Normal School and Clinic Control Values

Endurance Time (Percentile Level)	Percent of Patients: Normal Clinic Group	Normal School Group
<10th	21	47
11th to 25th	15	16
26th to 50th	26	16
51st to 75th	23	9
76th to 90th	11	7
>90th	3	5

valve disease—there were fewer than the expected number of patients having an exercise capacity above the 90th percentile. With the exception of six groups—patients with a mild ventricular septal defect, a mild or a moderate atrial septal defect, mild aortic stenosis, or post-rheumatic fever without valve lesions or with mild valve lesions—there were fewer than the expected number of patients with an exercise capacity above the 75th percentile range of normal.

The only groups of patients with heart defects in which no patient had an exercise capacity above the 50th percentile were those with tetralogy of Fallot before surgery, those with other lesions causing cyanosis and those with severe rheumatic valve disease. Even in these groups, 23, 7 and 53 percent of the subjects, respectively, had an exercise capacity in the 11th to 50th percentile range of normal. Figure 2 shows the chest roentgenograms of two children with serious heart problems with an above average exercise capacity and one child with transposition and a normal exercise capacity.

Comparison of patients with heart defects and normal school group: Table IV indicates a similar analysis of the patients with heart defects using values from the normal school group as control data. The mean values for endurance times in the schoolchildren were only 6 percent greater than for the normal clinic group, but the 10th and 25th percentile values were 12 to 15 percent greater for the schoolchildren. Because of the clustering of many patients in the lower range of normal, these differences in endurance times between the normal school and normal clinic groups made a considerable difference in the frequency of low exercise capacity values for the patient with heart defects. Children aged 4 and 5 years could not be used in the comparison in Table IV because data on these age groups were not collected in the schools.

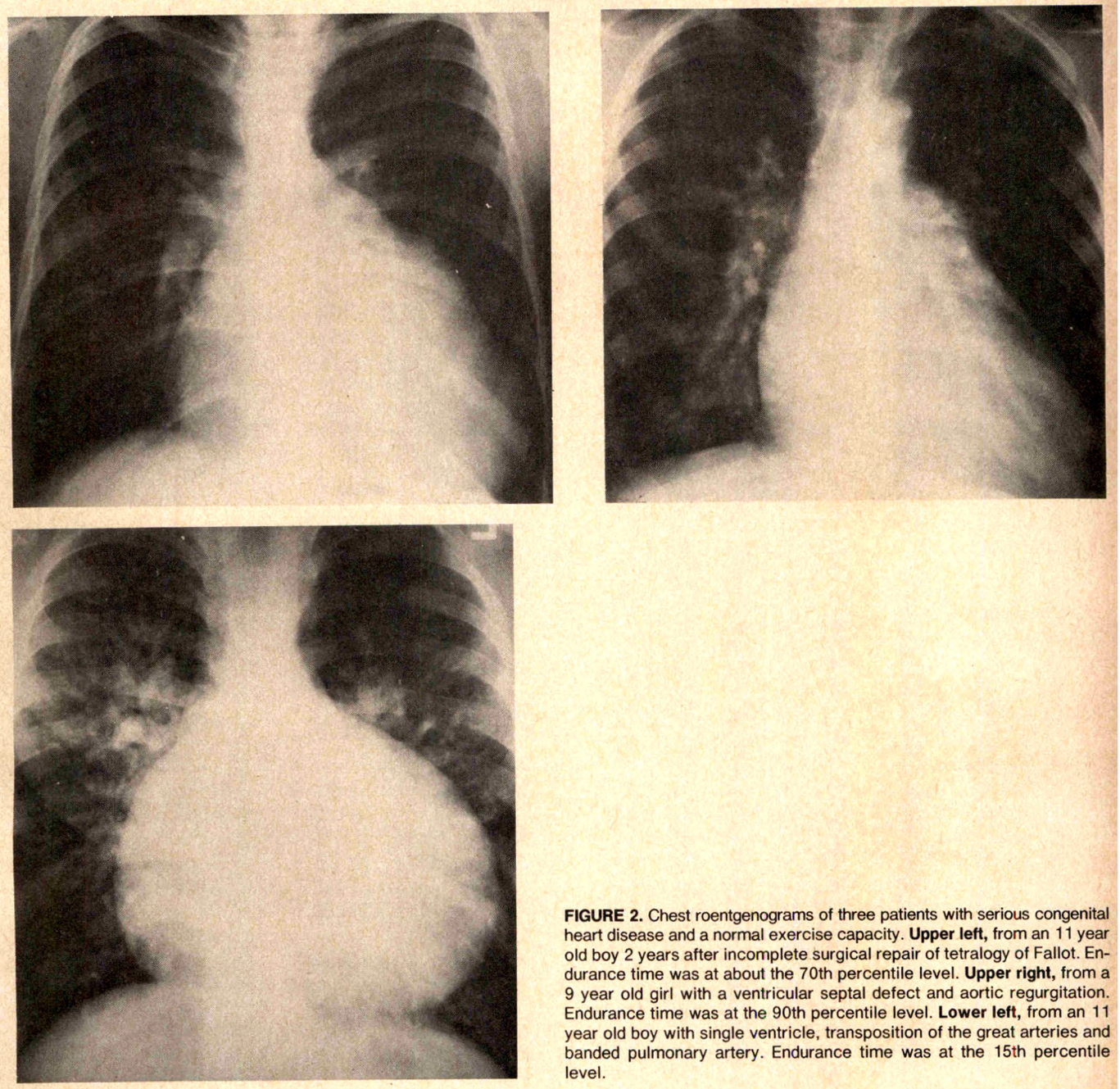


FIGURE 2. Chest roentgenograms of three patients with serious congenital heart disease and a normal exercise capacity. **Upper left,** from an 11 year old boy 2 years after incomplete surgical repair of tetralogy of Fallot. Endurance time was at about the 70th percentile level. **Upper right,** from a 9 year old girl with a ventricular septal defect and aortic regurgitation. Endurance time was at the 90th percentile level. **Lower left,** from an 11 year old boy with single ventricle, transposition of the great arteries and banded pulmonary artery. Endurance time was at the 15th percentile level.

A comparison of the overall categories of exercise capacity when the school and clinic series of normal subjects were used is shown in Table V, with 4 and 5 year olds eliminated from both series. When the values from the normal clinic group were used, 21 percent of the patients had an endurance time below the 10th percentile level, but when values from the normal school group were used 47 percent of the patients had an endurance time below the 10th percentile.

Discussion

Index of maximal exercise effort: The results of this study were dependent on how hard the subjects were willing to push themselves and on the ability, willingness and consistency of the technicians in urging children to produce a near maximal effort. Many children were able to perform considerably more exercise after reaching a heart rate of 180, 190 or even 200 beats/min; thus, a high heart rate alone was not a reliable indication of a maximal effort. An easily applied objective end point for clinical testing would be desirable. Measuring oxygen uptake to look for a plateau phenomenon is not a reliable and consistent technique because such a plateau is found in less than 50 percent of normal children.[6,7] Postexercise venous lactate was measured in many of our subjects, but the results showed considerable scatter and added little to the clinical assessment of whether the child made a near maximal effort.

There may be a subconscious tendency for techni-

cians to provide a patient with known significant heart disease less encouragement to work to exhaustion than that given to a normal subject, and parental or physician anxiety is easily transmitted to the patient or the technician, or both. Nearly all of our exercise studies were conducted by trained technicians in the absence of visual contact by the physician or parent but with a physician within 30 second's call and reach of the laboratory.

Exercise capacity and early exercise habits: The exercise capacity of the patients can be expected to be partly related to daily exercise habits. In this region of Canada the attitudes of the majority of pediatricians, family and school physicians and school officials are liberal concerning physical activity for children with heart defects. As a result, cardiac "nondisease,"[8] with children restricted because of innocent murmurs, is rarely encountered in this community. The majority of children with heart defects are allowed to regulate their own activities at play, during sports and during physical education. Only certain patients (that is, patients with moderate aortic stenosis) are advised against strenuous exercise activities or competitive athletics with a high cardiovascular component. School physical education and various training programs are overrated in their efficacy for improving the aerobic power of normally active children,[9] and some patients who were advised against competitive athletics and intense school activities had high levels of performance on the Bruce treadmill test. For example, one 13 year old boy with aortic stenosis and a peak pressure gradient of 35 mm Hg at rest completed 17 minutes of the Bruce treadmill test, and one 14 year old boy with childhood subendocardial fibroelastosis and persisting cardiomegaly and electrocardiographic changes had an endurance time of 16 minutes. Both of these boys had avoided competitive group sports all of their lives, but they did play tennis, ride a bicycle and take part in all recreational activities.

Exercise performance and body build: Aerobic exercise performance is in part genetically determined.[10] It is also related to body build because in both of our normal groups linear regression analyses relating endurance times to weight/height^3 and to body fat estimated from skinfold measurements indicated that up to 25 percent of the interindividual variations in endurance times were related to body build (unpublished observations). Ideally, normal percentile values should include a body build factor to take into account this variable in assessing exercise capacity.

Exercise times of normal subjects versus patients with heart defects: Although a major difference between the endurance trained athlete and an average normal person is the larger stroke volume of the athlete with the resulting greater maximal cardiac output and oxygen uptake, in any individual person the factor limiting exercise may be not the heart but skeletal muscle function.[11] Thus, mild cardiac impairment in persons of average physical training may not cause any obvious reduction in exercise performance even with maximal treadmill testing. If the fitness of the normal groups had been greater because of more intense physical activity programs, then fewer of the patients with heart defects would have had endurance times within the normal range. However, the endurance times for the normal subjects of 10 to 17 minutes for boys, and 9 to 14 minutes for girls, corresponded to estimated maximal oxygen uptake of 40 to 60 ml/kg per min for boys and of 28 to 54 ml/kg per min for girls. These values are equal to those found in the majority of population studies on children.[12,13]

The healthy myocardium of the young child with a structural heart defect is probably able to compensate for the extra cardiac work load required for intense exercise. The burden of the mechanical defect may lessen with exercise in some defects, such as aortic regurgitation, in which the regurgitant fraction may decrease with increases in heart rate,[14] and atrial septal defect, in which the percent of left to right shunt decreases during exercise in some patients.[15,16] Patients with a heart defect may partly compensate for a compromised oxygen transport system by greater peripheral extraction of oxygen and a wider arteriovenous oxygen difference.[17] The current study superficially monitored overall exercise performance, and no conclusions on hemodynamic mechanisms are possible.

In their California studies, Goldberg and co-workers[1,2] found that 90 percent of patients with heart defects had exercise scores lower than the 50th percentile level of normal subjects, and 69 percent had scores lower than the 3rd percentile, whereas only 61 and 21 percent of our patients with heart defects had endurance times below the 50th and 10th percentile ranges, respectively. We attribute the increased frequency of reduced exercise capacity in the California children with heart disease to the collection of normal values in the schools in these studies and the failure to encourage the patients with heart disease to exercise maximally. The latter point is supported by the high frequency of reduced maximal heart rates (mean maximal rate 170 beats/min) in the California studies, whereas maximal heart rates in our patients with heart defects were usually within the normal range (mean maximal heart rate 198 beats/min).

Normal clinic versus school control subjects: There is difficulty in knowing where to obtain control subjects for patient groups. To decide whether a reduction in exercise capacity is related to a disease state, the previous exercise habits of the control and patient groups should be similar, and ideally both groups should undergo similar conditioning programs. Our clinic series of normal children was possibly composed of more subjects with low exercise capacity because for some this may have led to their initial medical visit. The school series probably eliminated some of these children with a low capacity because these children did not return parental permission forms and so escaped the random selection method used. We consider the clinic series of normal subjects superior to the school series as a reference group for our patient group because the children were tested under exactly the same conditions as the patients over the same time span, and the school environment with peer competition provides a different motivational environment than the hospital clinic.

When compared with the normal schoolchildren, about 32 to 43 percent of patients with a small ventricular septal defect, previous rheumatic fever and no cardiac lesion, or mild pulmonary stenosis had an endurance time below the 10th percentile. These patients with mild lesions, or no lesion at all, would not be expected to have a low exercise capacity. When they were compared with the clinic series of normal children, only 6 to 11 percent of these same patients (the expected number) had an endurance time below the 10th percentile, thus supporting the use of the clinic series of normal subjects.

Limitations of maximal exercise testing: The limitation of maximal exercise tests in separating normal from abnormal conditions requires emphasis. Godfrey[18] suggested that exercise tests might be used to differentiate children with innocent murmurs from those with mild structural heart disease, but our data do not support this view. Of four girls tested on one recent afternoon, Patient 1, aged 4 years, with a ventricular septal defect and a pulmonary/systemic flow ratio of 2.7, had an endurance time of 10.8 minutes; Patient 2, aged 15 years, active in basketball and field hockey and a recent attendant at a summer sports training camp, had an endurance time of only 11 minutes despite having a clinically normal heart following earlier rheumatic fever; Patient 3, aged 8 years, with congenital atrioventricular block and a maximal ventricular rate of 93 beats/min, had an endurance time of 12.5 minutes; and Patient 4, aged 6 years, with an innocent heart murmur, had an endurance time of 12 minutes. Who was the more fit? All but Patient 2 were very slender, and Patient 2 was muscular but not obese; all seemed to have exerted themselves maximally and, except for Patient 3, all had a maximal heart rate of more than 200 beats/min.

The Bruce test has proved ideal for assessing exercise capacity in a pediatric clinic starting at age 4 years. The exercise test adds as little as 20 minutes to the patient's clinic visit. However, the treadmill endurance test did not separate mild from significant disease in patients with ventricular septal defect, atrial septal defect, pulmonary stenosis or aortic stenosis.

Implications: It is inappropriate to take a mean value for endurance time and label any deviation below the mean as "fitness aerobic impairment" as Bruce et al.[19] have done for adult subjects. Any deviation from the mean may have nothing to do with fitness or aerobics and may not be an impairment. We prefer to leave the data in percentile form, as for growth charts, to show parent and child how the endurance time of the child compares with that of others the same age tested in the same circumstances without any inference about impairment. Various studies in adult subjects with atrial septal defect and pulmonary stenosis[17,20–22] raise the possibility that exercise capacity below normal may be present in older patients with congenital heart disease, but for children with congenital heart defects only the most severely affected seem to have an exercise capacity on the treadmill that is definitely below that of children without heart defects.

Acknowledgment

Most of the exercise tests were carried out by D. Everatt, RN and L. Hastman, RT, with additional technical assistance by J. McCort, RT. The manuscript was prepared by M. Hornby.

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The Criss-Cross and Superoinferior Ventricular Heart: An Angiocardiographic Study

ROBERT M. FREEDOM, MD, FRCP(C), FACC
GORDON CULHAM, MD, FRCP(C)
RICHARD D. ROWE, MD, FRCP(Edin)

Toronto, Ontario, Canada

The angiocardiographic features of 11 patients with superoinferior and criss-cross type of atrioventricular (A-V) connections are presented. These unusual ventricular relations are thought to result from postseptation disturbances of ventricular looping. The angiocardiographic appearance of criss-cross is really an illusion, and the A-V connections among these patients are either concordant, discordant or straddling. The often small right A-V valve inflow and sinus portion of the ventricle, combined with the ventricular rotational anomaly, combine to give the angiocardiographic perception of criss-cross. A review of the 11 patients from this institution and those previously reported on suggests that most patients have a transposition or malposition of the great arteries; many have a small right ventricle, and about half have pulmonary outflow tract obstruction. In addition to the obvious embryologic, morphologic and clinical implications of these distorted ventricular loops, the criss-cross A-V hearts raise questions about the various segmental nomenclatures applied to these types of congenital heart disease.

Departures from the normal ventricular loop or the inverted ventricular relation are relatively uncommon.[1–4] However, in the past few years, increasing attention has been focused on patients with such distorted ventricular relations. These unusual ventricular relations have been given various designations, including mixed levocardia, superoinferior ventricles, criss-cross hearts, upstairs-downstairs ventricles, uncorrected levotransposition of the great arteries with associated ventricular rotation, corrected transposition of the great arteries with extreme counterclockwise torsion of the heart.[3,5–19]

These hearts, although uncommon, are more than a pathologic curiosity. They may be misdiagnosed at angiocardiography,[7] and they add another dimension to our understanding of atrioventricular (A-V) connections.[5,12] Furthermore, they serve to underscore the current controversies in the applications of a segmental nomenclature to the diagnosis of congenital heart disease.[20–27] We therefore report the angiocardiographic findings in 11 patients with a superoinferior ventricle and criss-cross heart, discuss the intrinsic morphologic features that may be anticipated in the setting of these disturbed ventricular relations, and examine the segmental nomenclatures applied to these ventricular loop malrotations.

Patient Material

The 11 patients who form the basis of this report underwent complete hemodynamic and angiocardiographic investigations at The Hospital for Sick Children. Postmortem findings were available in six patients. The 11 patients ranged in age from less than 1 day to 7 years at the time of angiocardiographic study. Only patients with levocardia or mesocardia are included in this analysis. Six of these 11 patients with ventricular loop malrotations had a superoinferior ventricular loop, and 5 had a criss-cross type of A-V connection. Although we

From the Division of Cardiology, Departments of Paediatrics, Pathology and Radiology, The Hospital for Sick Children, and Departments of Paediatrics, Pathology and Radiology, The University of Toronto, Toronto, Ontario, Canada. Manuscript received February 27, 1978; revised manuscript received May 15, 1978, accepted May 17, 1978.

Address for reprints: Robert M. Freedom, MD, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

think that the superoinferior ventricular relation and classic criss-cross heart share a similar embryogenesis and morphogenesis,[12,14] we have arbitrarily separated these patients into two groups on the basis of angiocardiographic appearance and will discuss their relevant pathologic and angiocardiographic findings separately.

Results

Pathologic Findings

Among the six patients studied at necropsy, levocardia was evident in five patients and mesocardia in one. All but one patient had visceroatrial situs solitus.

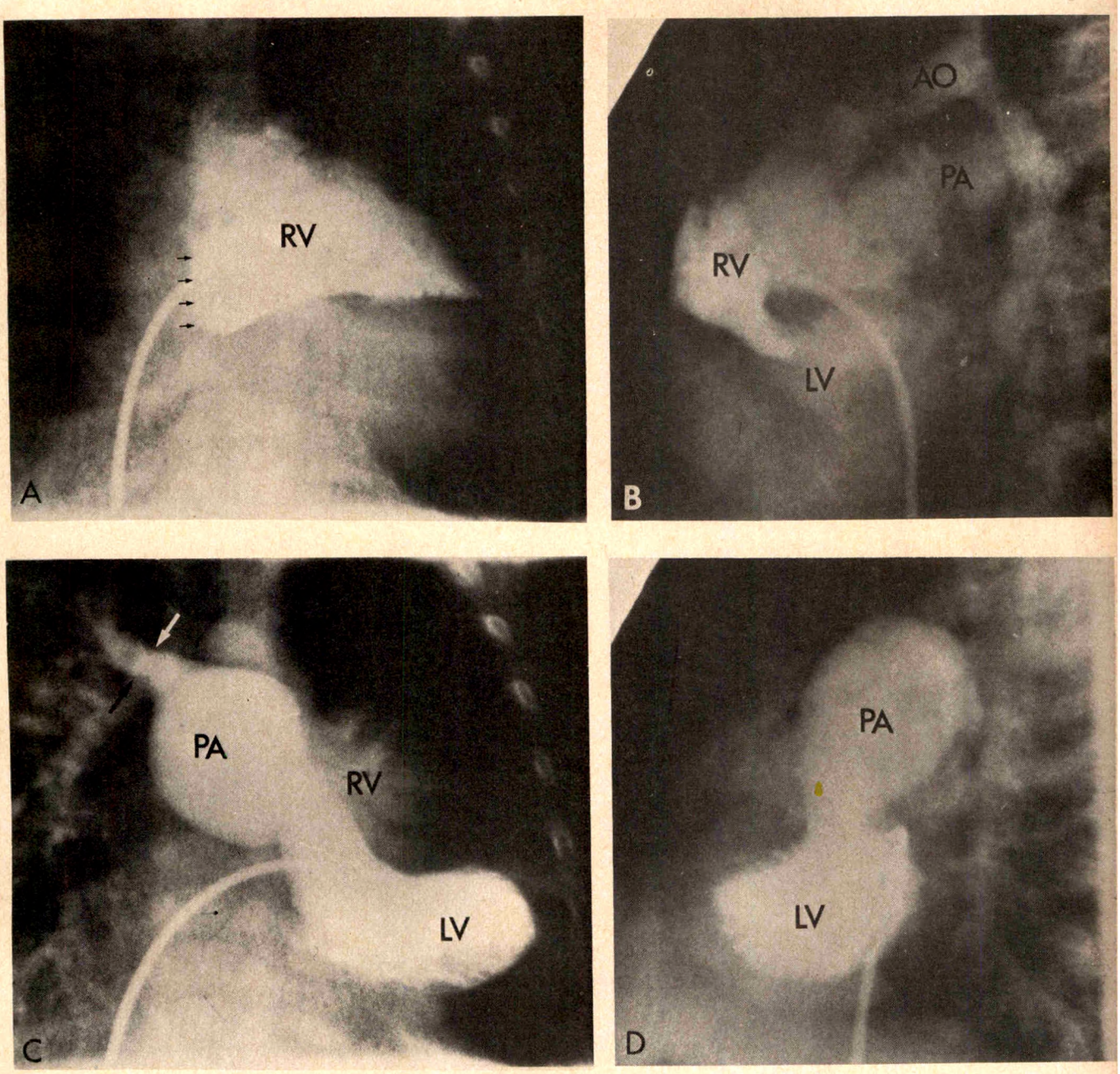


FIGURE 1. Angiocardiograms from a 5 month old child with atrial situs solitus, concordant A-V connections with a superoinferior ventricular relation, anteroposterior transposition of the great arteries and pulmonary arterial hypertension. **A,** anteroposterior projection of injection into superiorly placed, mildly underdeveloped right ventricle (RV). The tricuspid inflow **(black arrows)** is indicated. **B,** lateral view of this injection showing anteriorly placed, smaller transposed aorta (AO). The considerably larger pulmonary artery (PA) also opacifies on this injection. LV = left ventricle. **C,** anteroposterior injection into inferiorly positioned morphologically left ventricle. Although both great arteries opacify from this injection, the very dilated pulmonary artery (PA) is much more densely visualized. Right branch pulmonary arterial stenosis **(black and white arrows)** is also evident. The morphologically right ventricle is only faintly opacified. The inflow into this chamber is not clearly visualized on this injection. **D,** lateral projection of **C.** The posteriorly positioned pulmonary artery originates from the left ventricle. These features were confirmed at necropsy. Although the pulmonary artery originated above the left ventricle, pulmonary-mitral discontinuity resulted from interposition of 5.0 mm subpulmonary conus.

One patient demonstrated radiologic evidence of visceral heterotaxia with bilateral hyparterial bronchi. The abdominal inferior vena cava was right-sided and there was a right-sided azygos continuation to the right superior vena cava. A persistent left superior vena cava communicated with the coronary sinus, which returned to the right-sided atrium. Because the pulmonary veins connected with the left-sided atrium, this patient was considered to have situs solitus of the atria, despite the coexistence of visceral heterotaxia. Left juxtaposition of the atrial appendages was found in one patient.

The six patients studied at necropsy had concordant A-V connections, with atrial situs solitus and a D-ventricular loop. Thus the morphologically right atrium

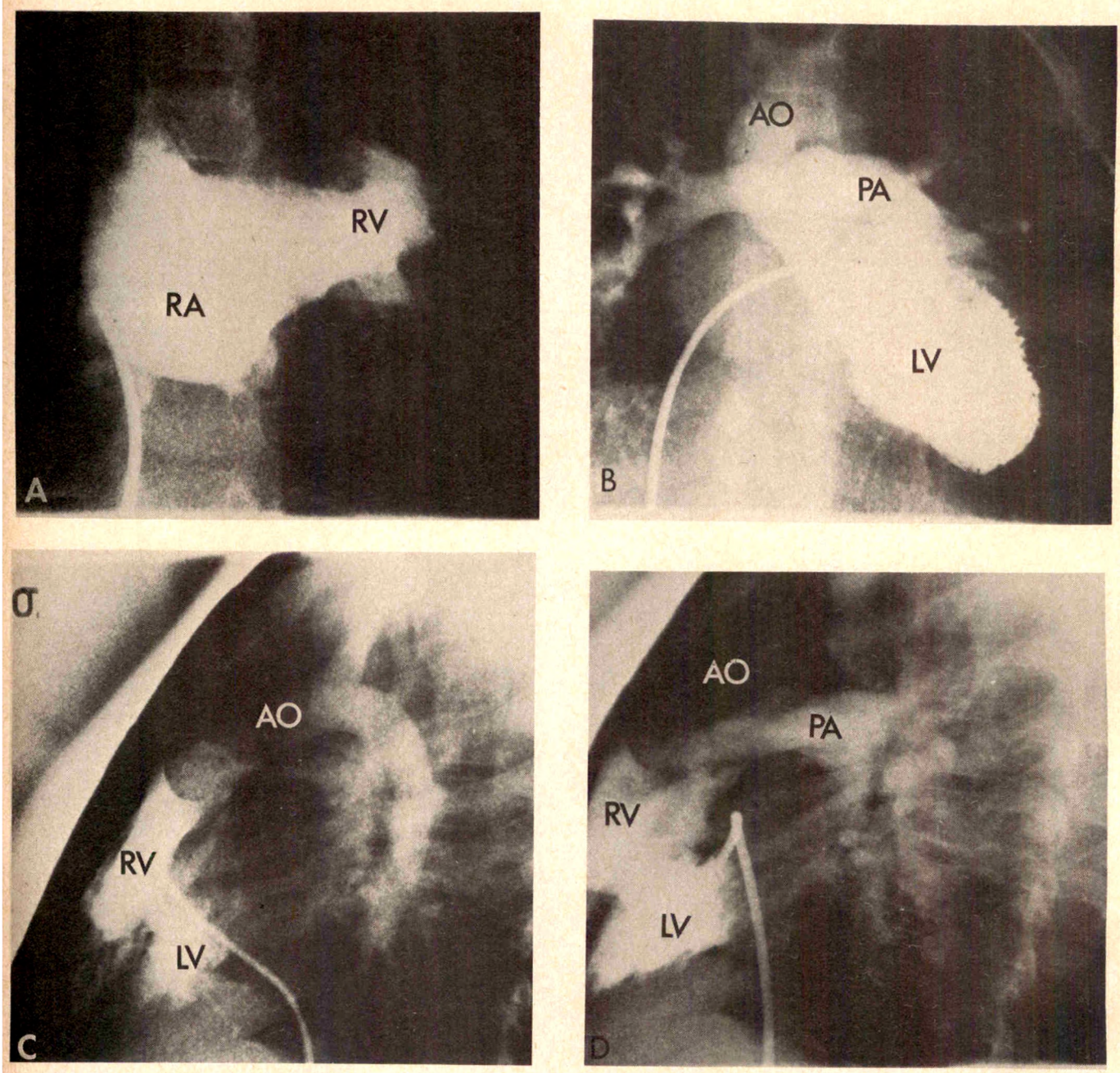


FIGURE 2. Angiocardiograms from a 6 year old boy with atrial situs solitus, concordant criss-cross A-V connections with D-ventricular loop, double outlet right ventricle, hypoplastic right ventricle and pulmonary outflow tract obstruction. **A,** right atrial (RA) injection with opacification of leftward positioned right ventricle (RV). The apical trabeculated portion of this chamber is grossly underdeveloped, but the inflow portion is well developed. **B,** anteroposterior projection of left ventriculogram with a catheter that entered by way of the posterior A-V valve. The morphologically left ventricle (LV) is well developed. The aorta (AO) lies to the right of the pulmonary artery (PA). The right ventricle is not clearly seen. **C,** lateral projection of right ventriculogram. This ventricle is significantly underdeveloped. In this frame, only the arteriorly positioned aorta opacifies. There is faint opacification of the more posteriorly positioned left ventricle. **D,** selective left ventriculogram in lateral projection. The right ventricle and both great arteries opacify by way of the ventricular septal defect. The pulmonary artery is better opacified than the aorta. Both great arteries originate from the right ventricle. This patient is alive, and from the angiocardiographic appearance the relation between the arterial roots and ventricular defect is unclear. The echocardiogram reveals discontinuity between the mitral valve and the posterior root.

communicated primarily with the morphologically right ventricle.[2,12,20,21] In the necropsy cases, the tricuspid valve was normally formed, but small in three; it was congenitally stenotic in one patient, and it straddled the ventricular septum in two. The right ventricle was small in all patients examined at necropsy. Specifically, the sinus portions and apical trabeculated portions appeared to be less well developed than the infundibular portion.

A ventricular defect was present in all six patients studied at necropsy. In three, the defect was membranous and in two it was intraconal with conal-ventricular septal malalignment; in one patient, both membranous and muscular defects were evident.

Obstruction to pulmonary blood flow was present in all but two of the six patients. Among patients with obstruction to pulmonary blood flow, both pulmonary valve and subvalve stenosis was present. One patient with severe aortic coarctation exhibited mild narrowing of his subaortic vestibule. This patient had transposition of the great arteries.

The great arteries were transposed or malposed in all six patients studied at necropsy. D-transposition was observed in one, L-transposition in four and double outlet right ventricle with D-malposition in one. A right-sided aortic arch was present in two. The ductus arteriosus was patent in one.

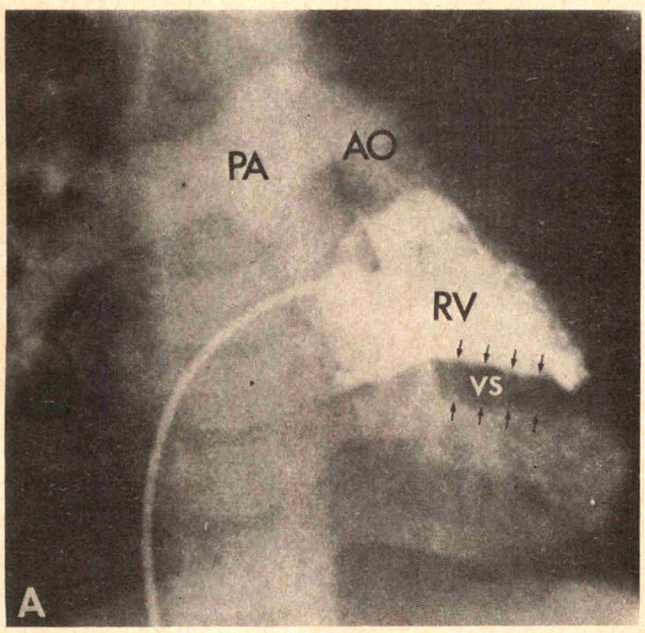
None of the six necropsy patients had anomalies of pulmonary venous connections. Similarly, the left A-V valve demonstrated only minor abnormalities, including mild thickening of the free valve margin in one, and thickened chordae from the anterior mitral leaflet in one patient. The anatomic features of all 11 patients as determined either at necropsy or on angiography, are shown in Table I.

TABLE I

Angiocardiographic and Necropsy Findings* in 11 Patients With Superoinferior Ventricle and "Criss-Cross" Heart

Findings	Patients (no. = 11)
Visceroatrial situs solitus	10
Visceral heterotaxia	1
Atrial situs solitus	11
Azygos continuation of inferior vena cava	1
Concordant (D-) ventricular loop	11
Hypoplasia of right ventricular sinus	9
Tricuspid valve hypoplasia	4
Tricuspid valve stenosis	1
Straddling tricuspid valve	2
Transposition of great arteries	9
D-related great arteries	2
L-related great arteries	6
AP-related great arteries	1
Double outlet right ventricle	1
Pulmonary outflow tract obstruction	9
Subaortic obstruction	1
Coarctation of aorta	1
Ventricular septal defect (not A-V canal)	11
Atrioventricular canal defect	1
Left juxtaposition of atrial appendages	1

* Necropsy was performed in six patients.
AP = anteroposterior.



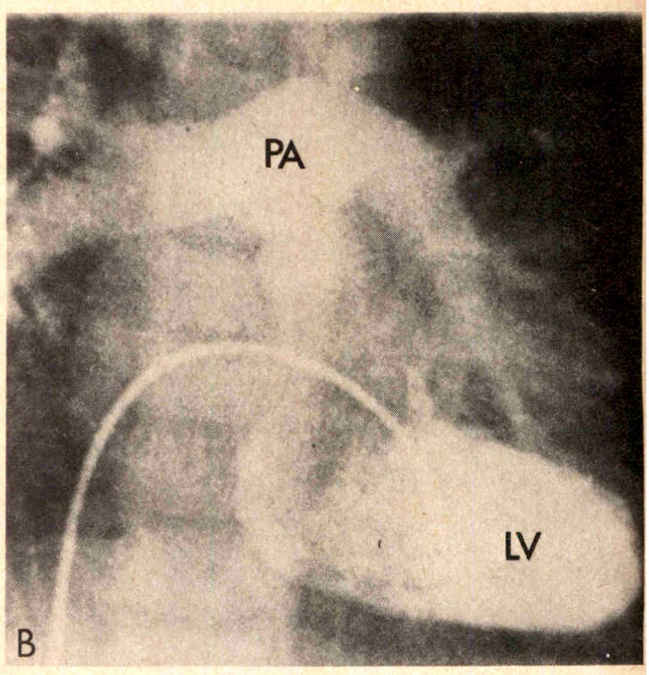


FIGURE 3. Angiocardiograms showing superoinferior ventricle with criss-cross A-V connections in a 6 month old child. There is atrial situs solitus, concordant A-V connections with a D-ventricular loop and transposition of the great arteries. The right ventricle (RV) is underdeveloped, and there is no pulmonary outflow tract obstruction. **A,** anteroposterior projection of injection into the smaller right ventricle. From this injection, both great arteries opacify, with the aorta (AO) to the left of the dilated pulmonary artery (PA). The plane of the ventricular septum (VS) is outlined **(arrows),** but the exact relation of the ventricular defect to the arterial trunks is not clearly defined. **B,** injection into the morphologically left ventricle (LV) entered by way of the posterior A-V valve opacifies the considerably larger left ventricle with subsequent opacification of the pulmonary artery. The ventricles appear in a superoinferior relation. The atrial injections confirm A-V concordance (not shown here). Although this patient is alive, the lateral angiocardiograms (not shown) suggest that the pulmonary artery originates entirely above the morphologically left ventricle.

Angiocardiographic Features

All 11 patients were studied with biplane cineangiocardiography, initially in the anteroposterior and lateral projections, but often in the oblique and occasionally in the caudally angulated projections as well. The data are shown in Table I.

A superoinferior ventricular relation was evident in six patients. As shown in Figures 1 to 3, the morphologically right ventricle was superior to the morphologically left ventricle. In these cases, there is no doubt that the superiorly positioned chamber is a morphologically right ventricle and that the posterior smooth-walled chamber is the left ventricle. As mentioned earlier, the morphologically right ventricle is frequently underdeveloped, with a small or distorted tricuspid valve and inflow portion, or both. Commonly, injection of contrast material into the inferior chamber will opacify the superior chamber and, unless an inflow portion to the superior chamber is clearly demonstrated, the superior chamber may be incorrectly considered an outlet or infundibular chamber and the patient may be thought to have single ventricle. Selective right atrial injection (Fig. 2A and 4A) should clearly demonstrate the mode of A-V connection.

In the five patients with the so-called criss-cross type of A-V connections, despite angiocardiographic evidence of atrial situs solitus and concordant A-V connections, the morphologically right ventricle appears to the left of the morphologically left ventricle, thus suggesting the presence of an inverted (or L-) ventricular loop and A-V discordance. As Van Praagh et al.[12] and others[5,8–11,13,18,19] have pointed out, this mode of A-V connection and its angiocardiographic appearance result from deficient counterclockwise ventricular rotation. Because of this lack of rotation, the plane of the ventricular septum appears to be at right angles relative to the plane of the atrial septum.[12] Furthermore, as shown in Figures 1 to 5, the inflow of the right ventricle is directed anteriorly and to the left, with the tricuspid valve being superior, rightward and slightly anterior relative to the mitral valve.[5,8–12] Hence the orientation of the A-V connection as visualized from the front and above gives the illusion of "criss-cross," with the right atrial-right ventricular connection anterosuperior to the left atrial-left ventricular connection.[12] As has been pointed out elsewhere,[12] the angiocardiographic appearance suggesting that the atria open into contralateral ventricles with criss-cross A-V connections is an illusion. The exact mode of A-V connections is readily apparent from the postmortem examination of such hearts designated angiocardiographically as criss-cross hearts.[3,5–19,28] Both the often relatively small inflow and sinus portion of the right ventricle and the postseptational ventricular rotation help to create this angiocardiographic appearance.[12]

Selective ventriculography may not adequately demonstrate the mode of A-V connection because of opacification of overlapping contiguous structures. Whereas selective ventricular angiocardiograms demonstrate the distorted ventricular relation, selective atriograms or levophase pulmonary arteriograms are frequently necessary to sort out which atrium connects to which ventricle (Fig. 2A and 5A). Because adequate angiocardiographic investigations of these patients may require five or six injections of contrast material (selective right and left ventriculograms, selective atriogram, selective aortic root angiogram to define epicardial distribution of coronary arteries and morphologic features and function of aortic valve, and pulmonary arteriogram), in some of these patients it has been necessary to perform the angiocardiographic investigation over 2 days to avoid contrast toxicity.

An unusual orientation of the ventricular septum is to be anticipated among patients with a superoinferior ventricular relation or criss-cross A-V connections. Because of the rotational deviation from normal of these ventricular loops, the plane of the ventricular septum is approximately at right angles relative to the plane of the atrial septum.[6,8–12] Among patients with a superoinferior ventricular relation, the ventricular septum may appear horizontal (Fig. 1, 3 and 4) and with criss-cross A-V connections, the ventricular septum is often best profiled in the anteroposterior projection (Fig. 1, 3 and 4). Our experience with axial cineangiography in the assessment of these malrotated ventricular loops is too limited to comment on the technique at this time.[29,30]

Discussion

Postseptational ventricular rotational anomalies add another dimension to the consideration of the embryology, morphology and nomenclature of these types of congenital heart disease. That these ventricular loop disturbances can be accurately diagnosed with selective atriography and ventriculography has been shown by our findings and those of others.[5–19] We have considered the angiocardiographic features and the morphologic implications of the superoinferior ventricular heart and the criss-cross heart together, cognizant of the implicit underlying distortion of the ventricular loop.[17] Yet, the most striking examples of criss-cross hearts are seen when the bodies of the ventricles are adjacent to each other (Fig. 4), not in a superoinferior relation, although there is obviously a continuum of such ventricular rotational anomalies.[5–19]

Anatomic profile (based on angiocardiographic and necropsy findings): Among previously reported cases with a superoinferior or criss-cross type of A-V connection, the visceroatrial situs is usually solitus; however, visceral heterotaxia was observed in one of our patients.[1–3,5–19] The heart usually occupies the left side of the chest, although one would certainly anticipate dextrocardia. Both concordant and discordant modes of A-V connection have been well described; our own series is obviously skewed with concordant connections. The morphologically right ventricle with its inflow is frequently underdeveloped, whereas the infundibulum often appears better expanded.[12] Including our own patients with criss-cross A-V connections, all patients have had a ventricular septal defect, usually large. The ventricular defect has usually been described as membranous, although we have observed defects involving

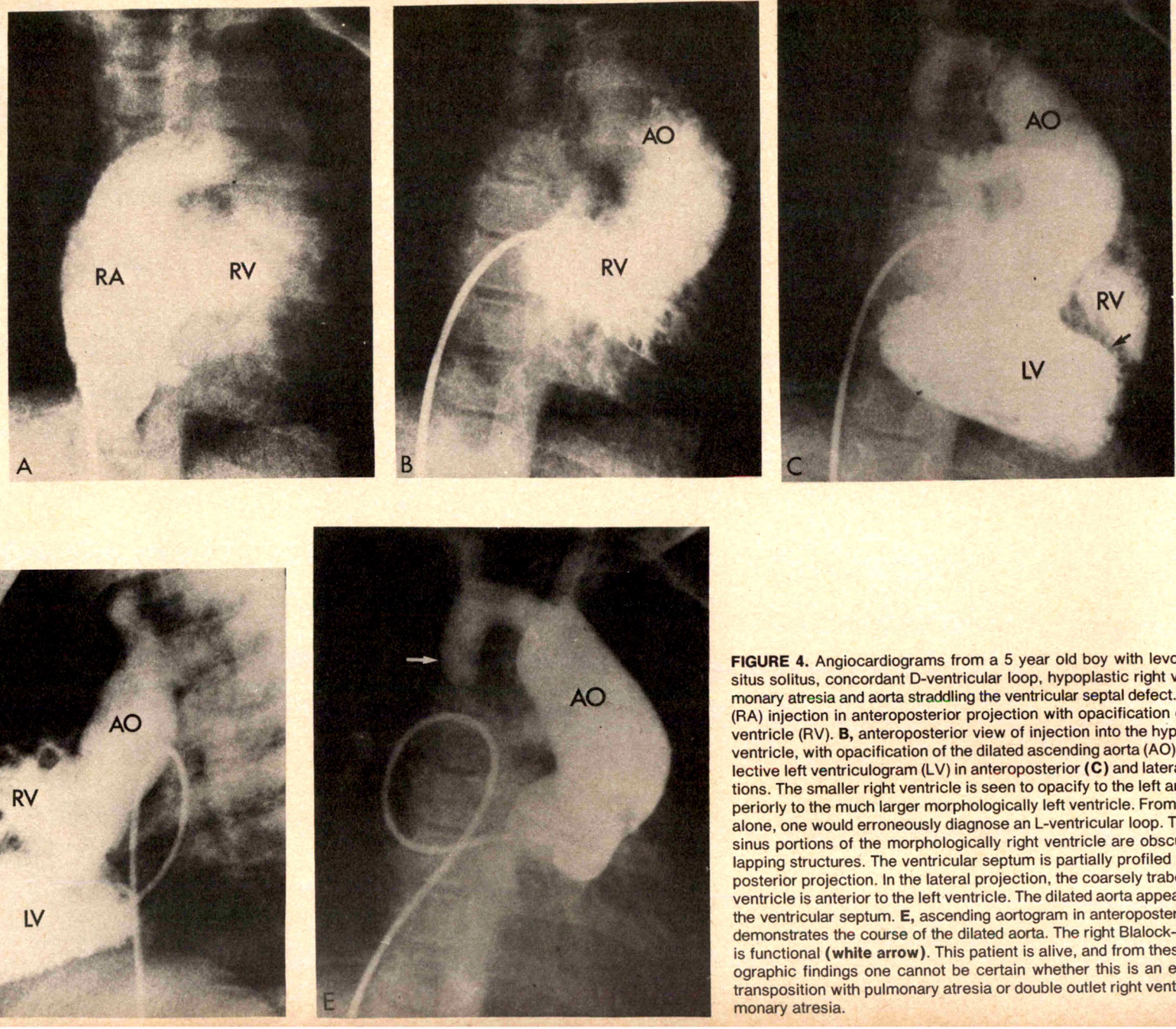


FIGURE 4. Angiocardiograms from a 5 year old boy with levocardia, atrial situs solitus, concordant D-ventricular loop, hypoplastic right ventricle, pulmonary atresia and aorta straddling the ventricular septal defect. **A,** right atrial (RA) injection in anteroposterior projection with opacification of small right ventricle (RV). **B,** anteroposterior view of injection into the hypoplastic right ventricle, with opacification of the dilated ascending aorta (AO). **C** and **D,** selective left ventriculogram (LV) in anteroposterior **(C)** and lateral **(D)** projections. The smaller right ventricle is seen to opacify to the left and slightly superiorly to the much larger morphologically left ventricle. From this injection alone, one would erroneously diagnose an L-ventricular loop. The inflow and sinus portions of the morphologically right ventricle are obscured by overlapping structures. The ventricular septum is partially profiled in the anteroposterior projection. In the lateral projection, the coarsely trabeculated right ventricle is anterior to the left ventricle. The dilated aorta appears to straddle the ventricular septum. **E,** ascending aortogram in anteroposterior projection demonstrates the course of the dilated aorta. The right Blalock-Taussig shunt is functional **(white arrow)**. This patient is alive, and from these angiocardiographic findings one cannot be certain whether this is an example of D-transposition with pulmonary atresia or double outlet right ventricle with pulmonary atresia.

the conal or infundibular septum, as well as defects of the A-V canal type. Transposition or some malpositioned relation of the great arteries is usually present. Only rarely are the great arteries normally connected.[14] The ventriculoarterial connections among patients with a criss-cross heart have recently been reviewed by Sato et al.[14] Pulmonary outflow tract obstruction is evident in about 50 percent of those with distorted ventricular loops, and the pathologic mechanisms responsible for this pulmonary stenosis include valve or muscular disease and, rarely, a ballooning membranous ventricular septum. Subaortic narrowing and obstructive anomalies of the aortic arch seem distinctly uncommon. Although there will certainly be departures from this profile, the angiocardiographic demonstration of such a distorted ventricular loop should alert one to exclude these morphologic implications. Although we have considered the angiocardiographic and pathologic features of the superoinferior ventricles and criss-cross heart separately, our findings and those of others suggest that the conditions do not have intrinsic embryologic or morphologic differences.[5–19]

The nature of "criss-cross" atrioventricular connections: As has been discussed elsewhere,[12] the appearance of "criss-cross" atrioventricular connections is an illusion[12]; that is, despite the angiocardiographic appearance, the right atrium communicates with the morphologically right ventricle (assuming concordant connections). Nonetheless, this mode of A-V connection in itself may suggest an abnormality of right ventricular inflow and the triscuspid valve.[5,7–19] The sinus portion of the right ventricle is frequently small, whereas the infundibular portion (derived from bulbus cordis) may seem better expanded.[12] The small inflow portion of right ventricle may be related to stenosis of the tricuspid valve, straddling of the tricuspid valve, or a normally formed but small tricuspid valve.[5–12,28,31]

Tricuspid valve disturbances: Although the right ventricle may have normal dimensions despite criss-cross A-V connections, angiocardiographic demonstration of such connections should alert one to the possibility of a functional and anatomic disturbance of the tricuspid valve. It should be emphasized that a hypoplastic right ventricular inflow and sinus alone do not lead to the angiocardiographic appearance of criss-cross A-V connections. The angiocardiographic features of classic pulmonary atresia and intact ventricular septum are well reported, and certainly these cases do not pose any difficulty regarding the mode of A-V connections. Similarly, the mode of A-V connection in the less severe form of hypoplastic left heart syndrome does not lead to confusion regarding the concordancy or discordancy of A-V connections. It is the lack of axial rotation, often combined with an abnormal right ventricular sinus, that is responsible for the heretofore described features.[12]

Clinical implications: In addition to the obvious embryologic and morphologic conclusions based on the study of hearts with disturbed A-V connections,[5,7,12,14,18,19] there are potentially clinically important implications as well. For example, if a patient with profound congestive heart failure is found to have a levotransposition relation between the great arteries and a large ventricular defect, pulmonary arterial banding could provide acceptable palliation in infancy. The levorelation of the aorta to the pulmonary artery would also suggest ventricular inversion or corrected transposition.[1,2,4] However, if the transposed aorta were in a levoposition because of criss-cross A-V connections, pulmonary arterial banding of even modest degree might significantly reduce the effective pulmonary blood flow, with subsequent hypoxemia. That is, if the A-V connections are concordant with transposition, pulmonary arterial banding has different implications than if A-V connections are truly discordant. Thus, recognition of this type of A-V connection has obvious therapeutic ramifications.

Role of segmental nomenclature in congenital heart disease: Although the term "criss-cross" heart, as introduced by Anderson and Ando and their colleagues in 1974[5,17] and shown diagrammatically in 1961 by Lev and Rowlatt,[3] is somewhat tantalizing, this descriptive adjective does not really illuminate the morphologic features of the heart. For some years, Van Praagh in a series of eloquent papers, de la Cruz and her colleagues and, more recently, Anderson and his colleagues have advocated a segmental approach to congenital heart disease, based on cardiac segments, connections, malformations and spatial position or relations.[1,2,5,7,12,20,22,23,25,26] Intrinsic to Van Praagh's segmental approach is the concept of the ventricular loop.[1,2,12,20,26] A D-loop has previously indicated a right-sided morphologically right ventricle and an L-loop, a left-sided morphologically right ventricle. Furthermore, Van Praagh et al.[1] suggested that the position of the great arteries at semilunar valve level was predictive of the ventricular loop (so-called loop rule). Thus, normally related or D-transposed great arteries would suggest the presence of a normal (or D-) ventricular loop, and the presence of L-transposed great arteries would suggest ventricular inversion. However, wide application of this loop rule has led to some obvious exceptions.[4,32–38] In view of these exceptions, and within the context of criss-cross A-V connections, what then is the role of a cardiac nomenclature based in part on ventricular loops, D- and L-?

The ventricular looping concept: To maintain a segmental nomenclature that could incorporate the criss-cross type of heart, Van Praagh et al.[12] recently restated some of the implications of ventricular looping. Intrinsic to the concept of a normal ventricular relation (or D-loop) is the observation that the internal organization of the ventricles is noninverted. In a D-ventricular loop, the internal organization of the "U" shaped morphologically right ventricle, from right to left, is (1) tricuspid valve; (2) sinus, body or inflow; (3) septal or moderator band; and (4) infundibulum.[12] Thus, using this implied refinement of the looping concept, with a concordant A-V connection of the criss-cross type, despite the unusual spatial relation of the trabeculated portions of the ventricles, the internal organization of the morphologically right ventricle suggests dextro-looping of the straight heart tube.

Within this restatement of the definition of ventricular loop (stressing the internal organization of the right ventricle), the criss-cross type of A-V connection is compatible with Van Praagh's segmental approach.[1,2,12,20] Yet as one views Figure 5, to many it would appear that this ventricular relation would result from L-ventricular looping. It is the overlapping of inflow, outflow and trabeculated portions of ventricles at angiocardiography that often makes the assessment of the precise mode of A-V connection difficult. Furthermore, despite the "normal" internal organization of the right ventricle in Figure 5C, one's perception is that the mass or bulk of the morphologic ventricle is left-sided, and thus one would erroneously conclude that ventricular inversion with discordant A-V connections is present. In this regard, pathologic appreciation of the mode of A-V connection in this type of heart is not difficult. The perception of A-V connections as "criss-cross" is angiocardiographic, not anatomic.

Incorporation of cardiac connections into the segmental approach: Others would argue that ventricular looping (and the identification of the ventricular loop as D- or L-) is not necessary to a logical and systematic approach to the segmental diagnosis of congenital heart disease.[5,7,22,23,25,27] Indeed, this is the position taken by Shinebourne, Anderson and their colleagues,[5,7,22,27] who in a series of papers have advocated *cardiac connections* rather than spatial relations, ventricular loops or conal morphologic features as their primary criterion in sequential chamber localization. As part of their segmental approach, these authors prefer to identify A-V connections as concordant or discordant when the atrial situs is known. They admit, however, that these terms are not justified in the setting of visceroatrial heterotaxia and an indeterminate atrial situs, double inlet ventricle and in major degrees of A-V valve straddling. In the setting of visceroatrial heterotaxia, Shinebourne and his colleagues[22,23] would employ the terms D-loop and L-loop when two ventricles are present.

The advantage of the ventricular looping concept, and the refinement concerning the internal organization of the right ventricle, is that the definition of the ventricular loop is independent of atrial situs or straddling A-V valve. One could argue that the appreciation of the right ventricular inflow in the setting of criss-cross A-V relations requires a sophistication that would preclude the widespread application of such a nomenclature. However, that is debatable. Nonetheless, despite considerable prose suggesting the contrary, these didactic approaches to the segmental nomenclature of congenital heart disease, with their various constituencies, share in large part a common ground. We believe that the arguments of Anderson and his colleagues favoring the incorporation of cardiac connections into the segmental approach are persuasive but that cardiac connections do not mutually exclude the very important concept of looping, and vice versa.[39,40] What is now needed is a common framework of segmental nomenclature that will facilitate an ongoing dialogue among those concerned with the various disciplines of congenital heart disease.

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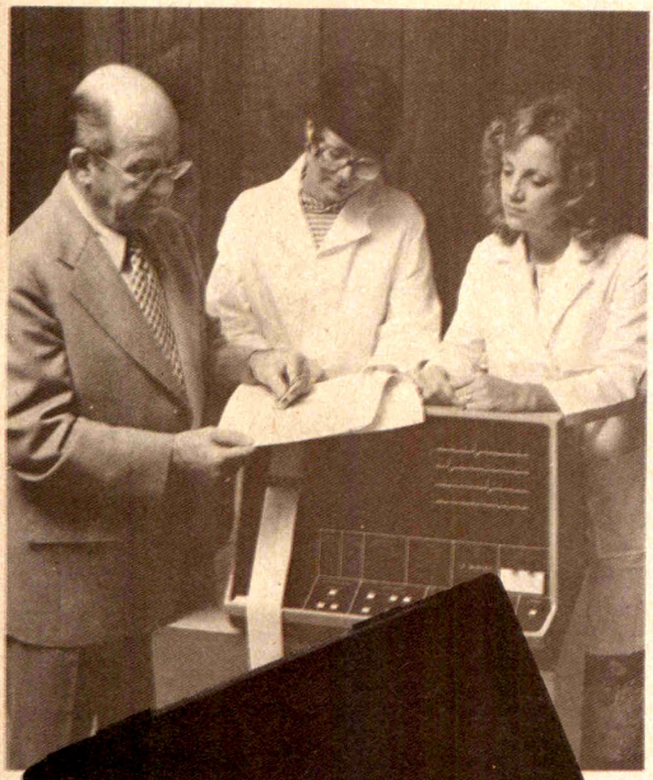
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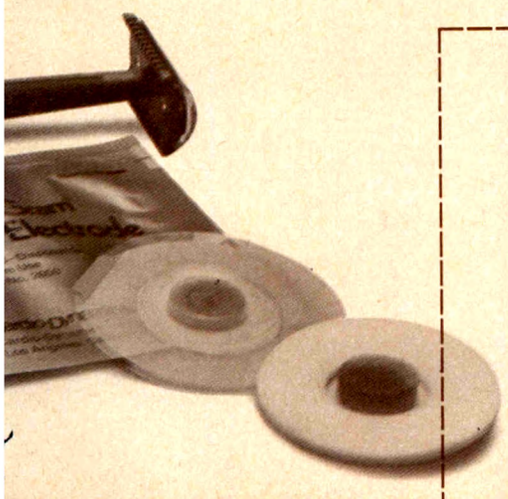
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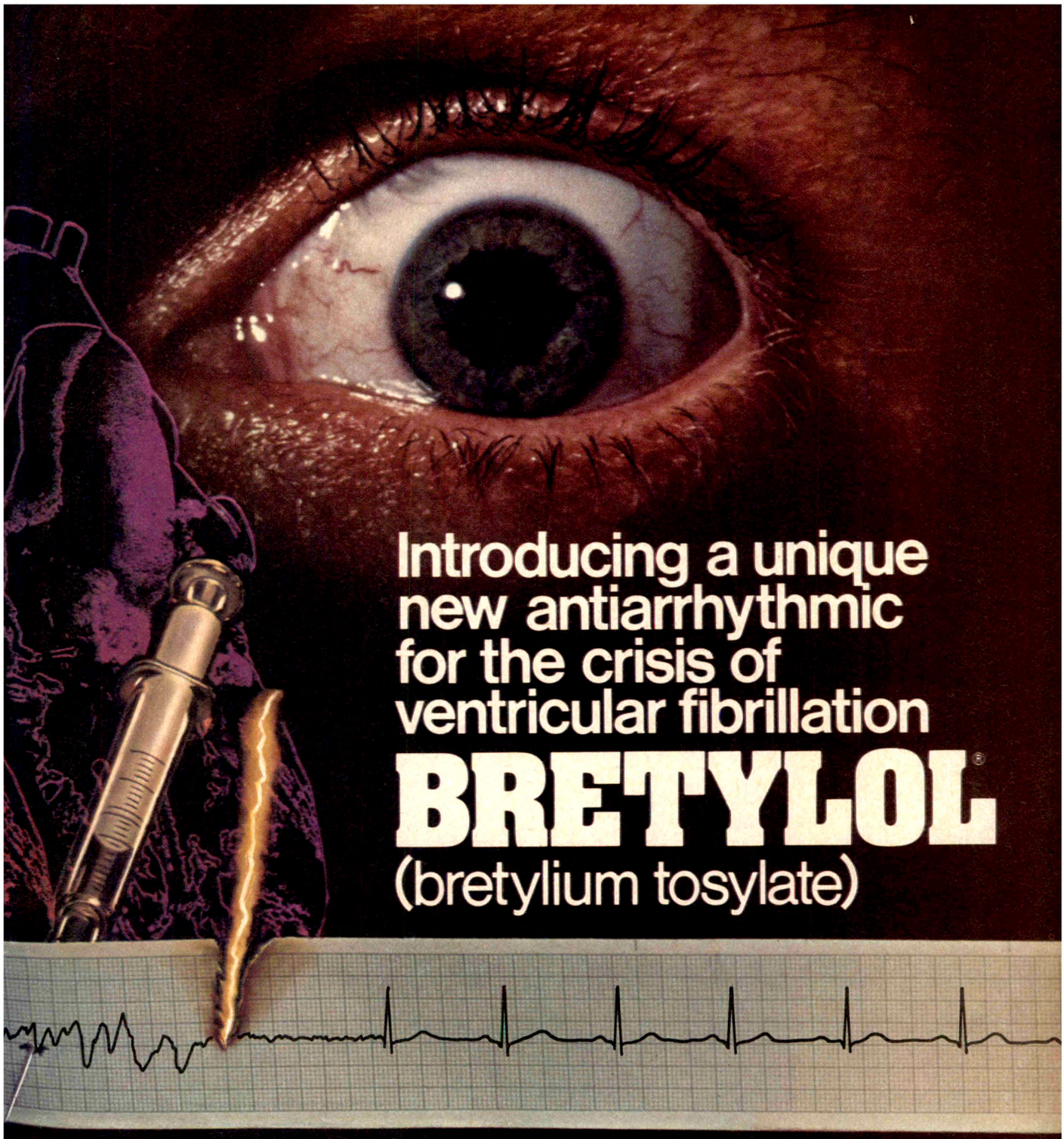
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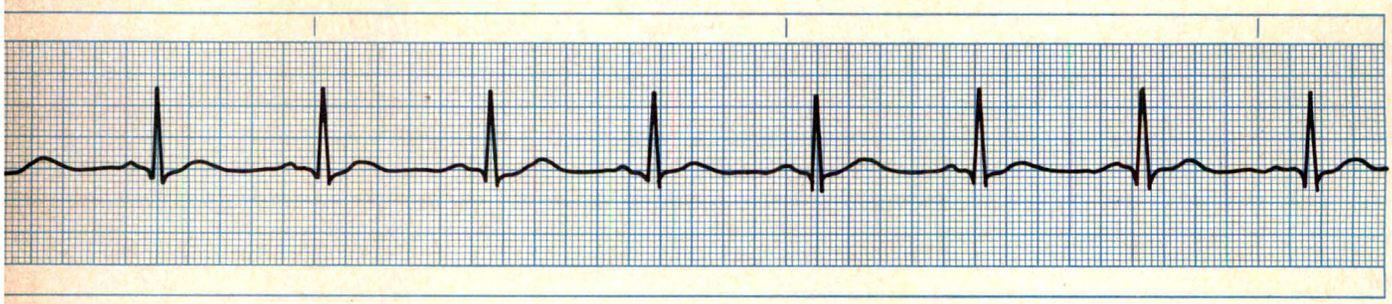
Due to the initial release of norepinephrine from the adrenergic postganglionic terminals, there may be initial *transient* increases in blood pressure, heart rate and/or PVC's. These generally return promptly to preadministration levels.

Nausea and vomiting can usually be obviated by the slow intravenous administration of a dilute solution of BRETYLOL.

For a full description of adverse reactions, please refer to the complete prescribing information on the last page of this advertisement.

ARNAR-STONE LABORATORIES, INC.

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BRETYLOL® bretylium tosylate

BRETYLOL® (bretylium tosylate) Bibliography

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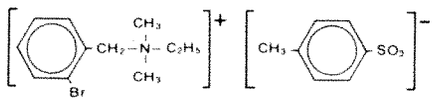
BRETYLOL bretylium tosylate

BRETYLOL INJECTION

FOR INTRAMUSCULAR OR INTRAVENOUS USE

DESCRIPTION

BRETYLOL (bretylium tosylate) is o-Bromobenzyl ethyldimethylammonium p-toluene sulfonate. The chemical structure is:



$C_{18}H_{24}BrNO_3S$ Mol. Wt. 414.39

BRETYLOL is a white, crystalline powder with an extremely bitter taste. It is freely soluble in water and alcohol. Each ml of sterile, pyrogen-free solution contains 50 mg bretylium tosylate in Water for Injection, USP. The pH is adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. BRETYLOL contains no preservative.

CLINICAL PHARMACOLOGY

BRETYLOL (bretylium tosylate) is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

BRETYLOL also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibillation threshold.

2. Increase in action potential duration and effective refractory period without changes in heart rate.

3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.

4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by BRETYLOL, but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because BRETYLOL causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, BRETYLOL blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of BRETYLOL and peak hypotensive effects were seen within one hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6-9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. No metabolites have been identified following administration of BRETYLOL in man and laboratory animals. In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose is excreted in the urine during the first 24 hours, with an additional 10% excreted over the next three days.

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does appear to be digitalis toxicity and other antiarrhythmic drugs are not ef tive. Simultaneous initiation of therapy with digitalis glycosi and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed car output (i.e., severe aortic stenosis or severe pulmonary hypertens BRETYLOL should be avoided since severe hypotension may result fro fall in peripheral resistance without a compensatory increase in car output. If survival is threatened by the arrhythmia, BRETYLOL may be u but vasoconstrictive catecholamines should be given promptly if se hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been establis However, as the drug is intended for use only in life-threatening situation may be used in pregnant women when its benefits outweigh the poter risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been establis BRETYLOL has been administered to a limited number of pediatric patie but such use has been inadequate to define fully proper dosage and lim tions for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be diluted (one BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chlo Injection, USP) prior to intravenous use. Rapid intravenous administra may cause severe nausea and vomiting. Therefore, the diluted solution sh be infused over a period greater than 8 minutes. In treating existing vent ular fibrillation BRETYLOL should be given as rapidly as possible and r be given without dilution.

2. Use Various Sites for Intramuscular Injection: When injected tramuscularly, not more than 5 ml should be given in a site, and inject sites should be varied since repeated intramuscular injection into the sa site may cause atrophy and necrosis of muscle tissue, fibrosis, vasc degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL excreted principally via the kidney, dosage should be reduced in patie with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently ported adverse reactions (see Warnings section). Nausea and vomiting curred in about three percent of patients, primarily when BRETYLOL w administered rapidly by the intravenous route (see Precautions sectio Vertigo, dizziness, light-headedness and syncope, which sometimes acc panied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractio transitory hypertension, initial increase in arrhythmias (see Warnings sectio precipitation of anginal attacks, and sensation of substernal pressure ha also been reported in a small number of patients, i.e., approximately patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous m ular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotio lability, lethargy, generalized tenderness, anxiety, shortness of breath, d phoresis, nasal stuffiness and mild conjunctivitis, have been reported about 1 patient in 1000. The relationship of BRETYLOL administration these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of life-threateni ventricular arrhythmias under constant electrocardiographic monitoring. Sin there is a delay in onset of its antiarrhythmic action, BRETYLOL is not to considered or used as a replacement for rapidly-acting antiarrhythmic agen currently in use. The clinical use of BRETYLOL is for short-term use or Patients should either be kept supine during the course of BRETYLOL th apy or be closely observed for postural hypotension. The optimal dose sch ule for parenteral administration of BRETYLOL has not been determin There is comparatively little experience with dosages greater th 30 mg/kg/day, although such doses have been used without apparent verse effects. The following schedule is suggested:

A. For Immediately Life-threatening Ventricular Arrhythmia, as Ventricular Fibrillation: Administer undiluted BRETYLOL at a dosage 5 mg/kg of body weight by rapid intravenous injection. Other usual card pulmonary resuscitative procedures, including electrical cardioversion, shou be employed prior to and following the injection in accordance with good medi practice. If ventricular fibrillation persists, the dosage may be increased to mg/kg and repeated at 15 to 30 minute intervals until a total dose of not m than 30 mg/kg of body weight has been given. For maintenance dosage, s below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as follows bef intravenous administration:* Using aseptic technique, dilute contents one BRETYLOL ampul (10 ml containing 500 mg bretylium tosylate) to minimum of 50 ml with Dextrose Injection, USP or Sodium Chloride inje tion, USP.

Administer the diluted solution at a dosage of 5 to 10 mg BRETYLOL p kg of body weight by intravenous infusion over a period greater than 8 mi utes. More rapid infusion may cause nausea and vomiting. A second do may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: (*Do not dilute BRETYLOL prior to int muscular injection.*) Inject 5 to 10 mg BRETYLOL per kg of body weig Dosage may be repeated in 1 to 2 hours if the arrhythmia persists. The after maintain with same dosage every 5 to 8 hours.

Intramuscular injection should not be made directly into or near a ma nerve, and the site of injection should be varied on repeated injection.

C. Maintenance Dosage: The diluted BRETYLOL solution may be admi istered by intermittent bolus infusion or by constant infusion.

1. Intermittent Infusion: Infuse the diluted solution at a dosage of 5 to mg BRETYLOL per kg body weight, over a period greater than 8 minut every 6 hours. More rapid infusion may cause nausea and vomiting.

2. Constant Infusion: Infuse the diluted solution at a dosage of 1 to 2 BRETYLOL per minute.

Dosage of BRETYLOL should be reduced and discontinued in 3 to 5 da under electrocardiographic monitoring. Other appropriate antia rhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate Water for Injection, USP, pH adjusted, when necessary, with dilute hydr chloric acid or sodium hydroxide. Sterile, pyrogen-free. July 19

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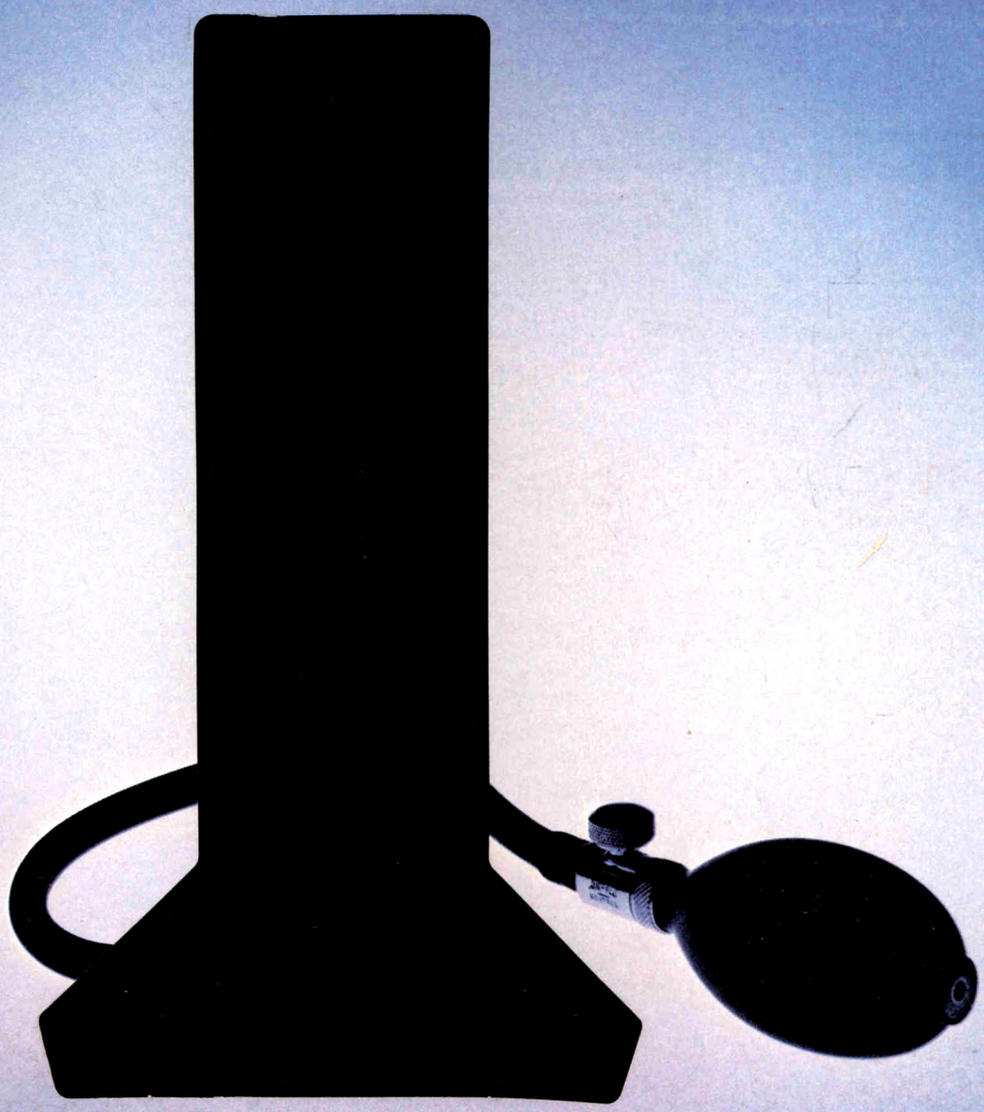
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MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

YEARS OF BLOOD PRESSURE CONTROL...

- Effectively controls blood pressure over the long term* without compromisin cardiac or renal function. Reflex tachycardia frequently associated with othe vasodilators is much less common with Minipress.
- Effective Step 2 antihypertensive agent when combined with a diuretic.
- Effectiveness enhanced when combined with a diuretic and/or other antihypertensive agents.
- Limited potential for organ toxicity. Laboratory abnormalities such as positive Coombs' tests have not been a problem with Minipress therapy.
- Few persistent side effects. The most common reactions have generally been mild and transient: dizziness, headache, drowsiness, lack of energy, weakness, palpitations, nausea. A small percentage of patients have experienced orthostatic hypotension and syncope.
- Rarely compromises sexual function.
- Compatible with many medications administered for concomitant diseases

WITHOUT COMPROMISE OF VITAL ORGANS



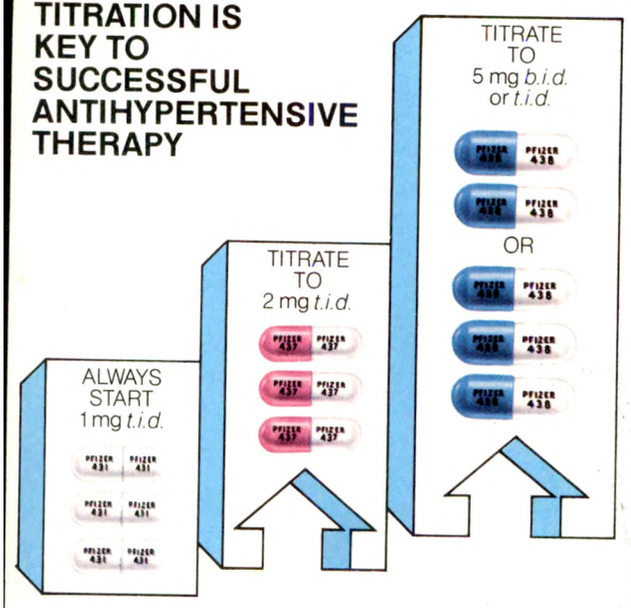
Please see Brief Summary on last page.
Before prescribing Minipress, WARNINGS and DOSAGE AND ADMINISTRATION sections should be carefully reviewed.

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(prazosin HCl)

YEARS OF BLOOD PRESSURE CONTROL...WITHOUT COMPROMISE OF VITAL ORGANS

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

TITRATION IS KEY TO SUCCESSFUL ANTIHYPERTENSIVE THERAPY



USUAL MAXIMUM DAILY DOSAGE: 20 mg given in divided doses *(b.i.d.* or *t.i.d.)*. A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

- **Initial therapy:** Whether using Minipress in combination with other agents or alone, the starting dosage is 1 mg *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *t.i.d.*
- **Dosage titration:** Thereafter, titrations of Minipress should be carried out according to patient response. Dosage may be slowly increased to a daily maximum of 20 mg given in divided doses. Although some patients may be controlled on 1 mg *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients in order to achieve optimal blood pressure control.
- **Maintenance therapy:** After initial titration, patients may be maintained on a *b.i.d.* or *t.i.d.* dosage regimen.
- If optimum control is not achieved in patients receiving Minipress and a diuretic, consider adding another Step 2 antihypertensive agent.
- If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic.
- When adding a diuretic or other antihypertensive agent, Minipress dosage should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.
- Available in 1-mg, 2-mg, and 5-mg capsules.

REMOVE PAGE AND FOLD ALONG DOTTED LINE AND SAVE FOR REFERENCE

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit-dose institutional packages of 100 (10 x 10's).

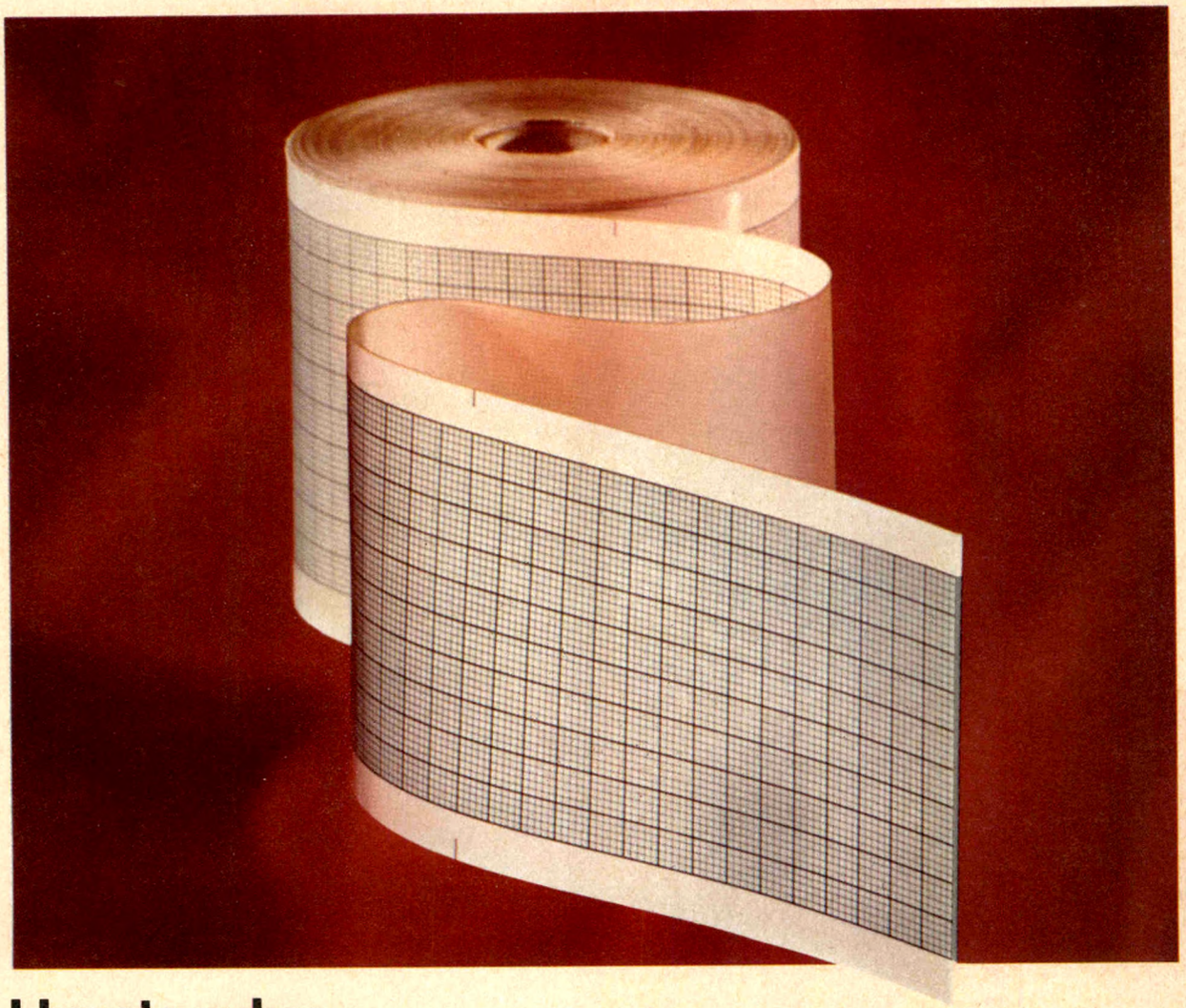
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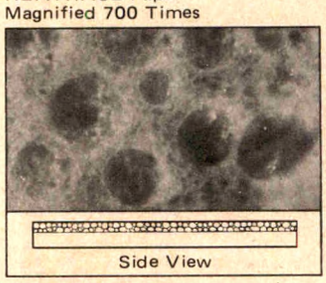
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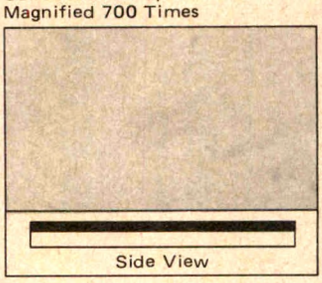
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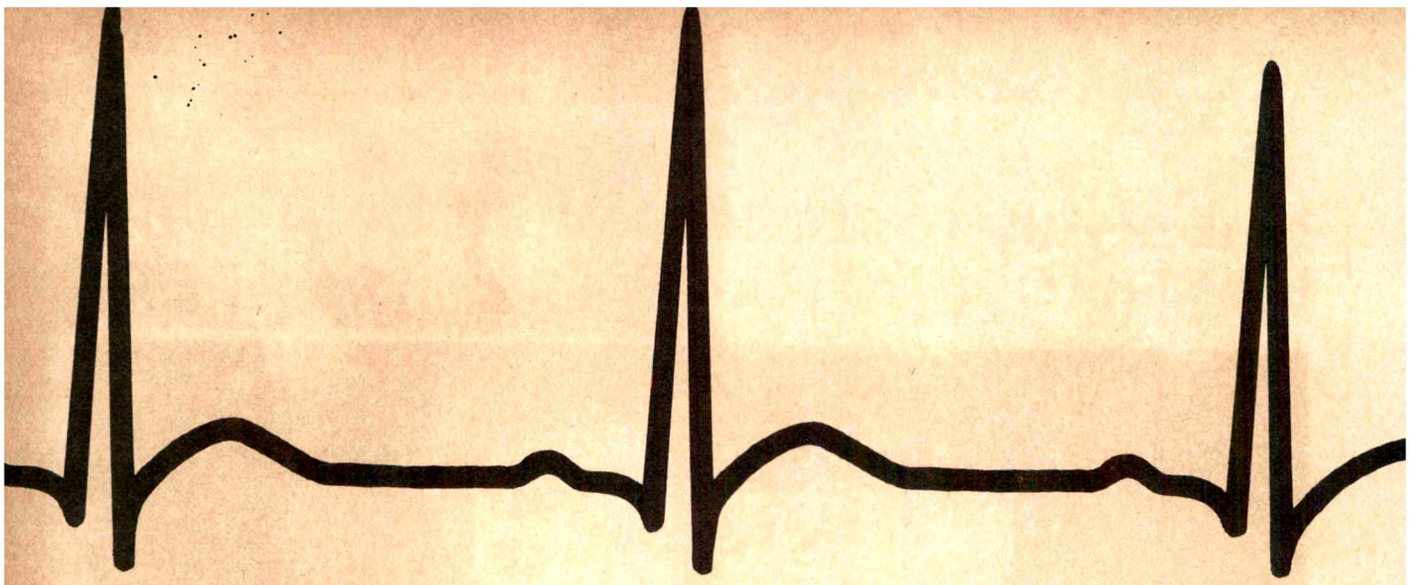
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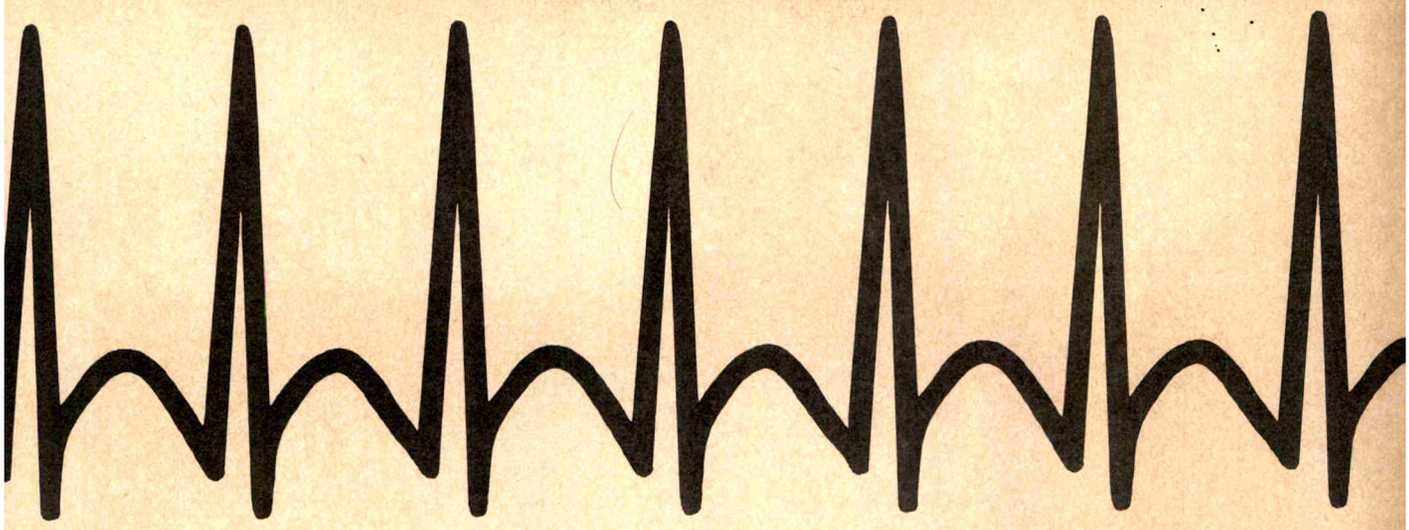
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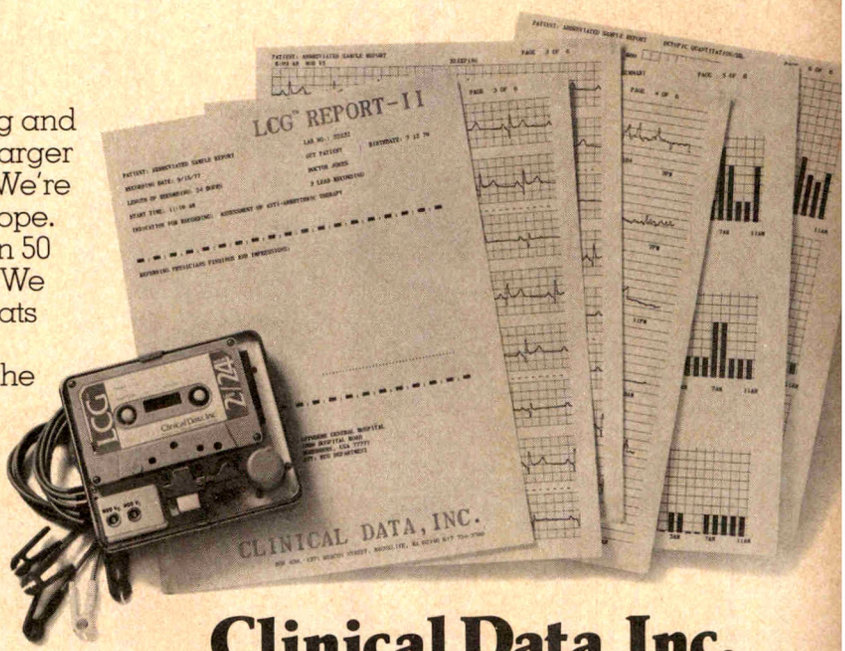
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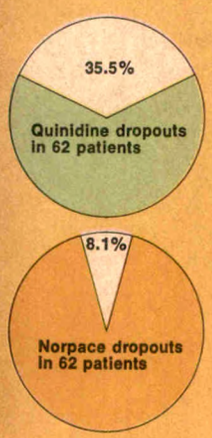
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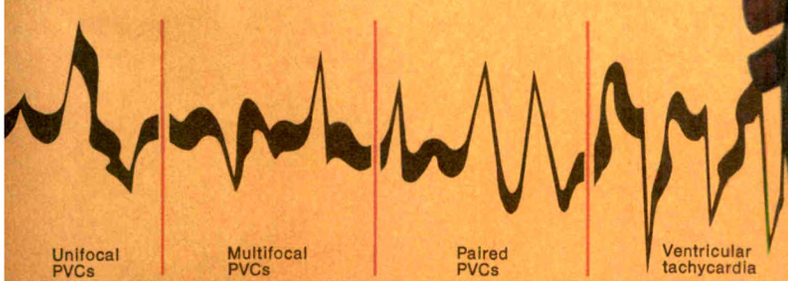
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Dose-related plasma levels—Plasma levels correlate closely with dosage.

Norpace (disopyramide phosphate) effect on hemodynamics—Rarely alters blood pressure significantly at recommended doses. May reduce cardiac output by about 10%.

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:
Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished.

In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained with appropriate treatment. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction, evidenced by widening of the QRS complex and/or prolongation of the Q-T interval.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

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Initial Norpace dosage

Patients 110 lb or more	150 mg q 6 h
Patients less than 110 lb	100 mg q 6 h
Patients with specific complications: Patients with *possible cardiac decompensation, cardiomyopathy, reduced left ventricular function* or *hypotension* due to these or other causes	100 mg q 6 h
Patients with moderate renal impairment ($C_{Cr} > 40$ ml/min) or hepatic insufficiency	100 mg q 6 h (200-mg loading dose optional)
Patients with severe renal insufficiency ($C_{Cr} < 40$ ml/min)	100 mg given approximately every half-life (T½) (200-mg loading dose optional)
C_{Cr} = 40–15 ml/min	q 10 h
C_{Cr} = 15– 5 ml/min	q 20 h
C_{Cr} = 5– 1 ml/min	q 30 h
In patients *without the complications* specified above in whom rapid control of arrhythmias is essential, therapy may be initiated with a loading dose of 300 mg (200 mg for patients under 110 lb).	

For complete Norpace dosage recommendations, please see complete prescribing information, a brief summary of which appears below.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy. *Use in Pregnancy and Lactation:* Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, hypoglycemia, (usually in patients with impaired liver function), and dysuria. Acute psychosis and cholestatic jaundice, both reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

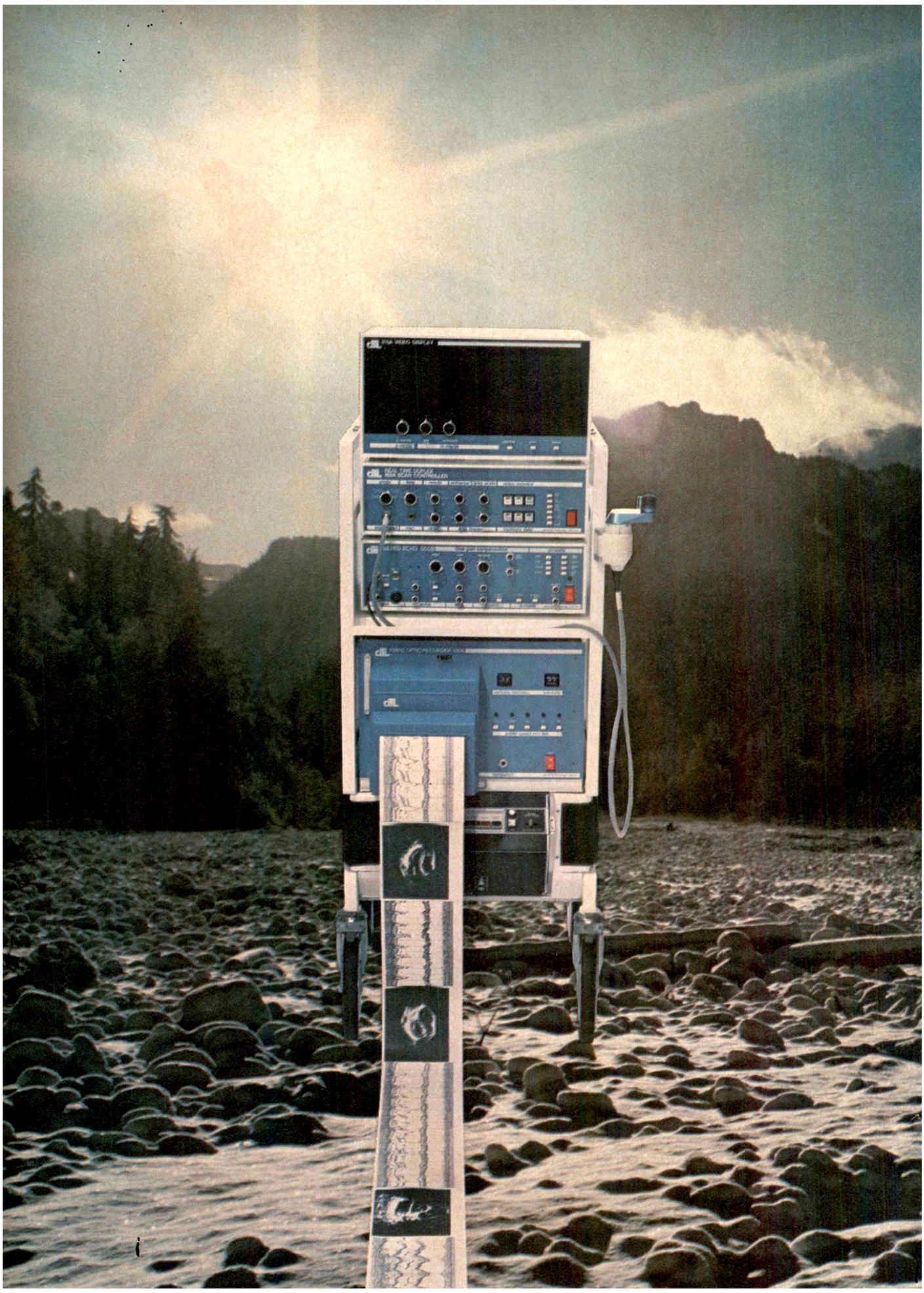
See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

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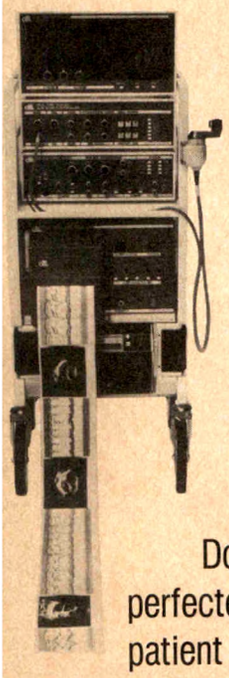
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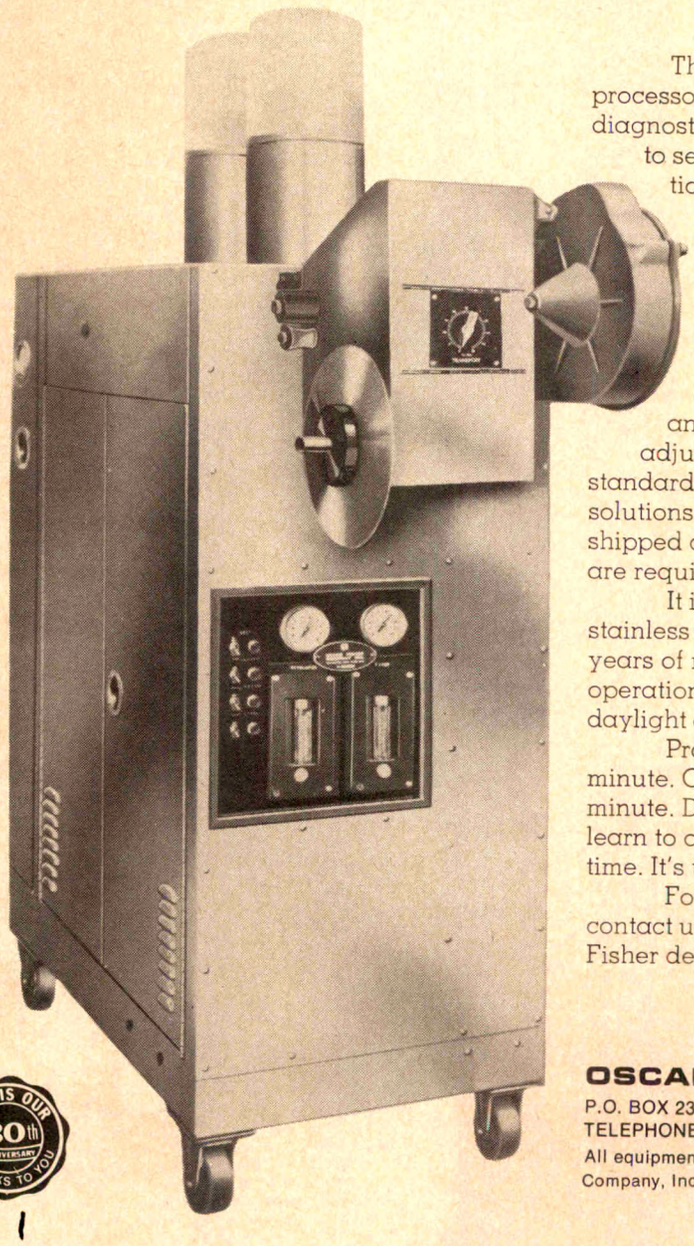
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Surgical Approach for Patients With Unstable Angina Pectoris: Role of the Response to Initial Medical Therapy and Intraaortic Balloon Pumping in Perioperative Complications After Aortocoronary Bypass Grafting

RENE A. LANGOU, MD, FACC
ALEXANDER S. GEHA, MD, FACC
GRAEME L. HAMMOND, MD, FACC
LAWRENCE S. COHEN, MD, FACC

New Haven, Connecticut

The role of the response to initial medical therapy and intraaortic balloon pumping in perioperative complications was evaluated in 194 consecutive patients with unstable angina pectoris who underwent cardiac catheterization and coronary surgery from July 1975 through December 1977. Sixty-four patients (33 percent) responded to medical therapy within 48 hours after the initiation of full medical therapy in the coronary care unit and underwent elective cardiac catheterization and coronary surgery; 130 patients (67 percent) did not respond to medical therapy. Of these 130 patients, 75 (58 percent) received the preoperative assistance of an intraaortic balloon pump and underwent emergency cardiac catheterization and surgery. Fifty-five patients (42 percent) of the medical nonresponders were not treated with an intraaortic pump and underwent emergency cardiac catheterization and surgery. Chi square analysis revealed that the clinical characteristics of the patients in all three groups were similar.

The overall rate of operative mortality was 6.1 percent. Medical responders had no operative mortality, medical nonresponders with intraaortic balloon pumping had an operative mortality rate of 5.3 percent and medical nonresponders without balloon pumping a rate of 14.5 percent. The overall incidence rate of perioperative myocardial infarction was 13 percent; it was 6 percent in medical responders, 6.6 percent in nonresponders with intraaortic balloon pumping and 29 percent in nonresponders without intraaortic balloon pumping. Thus, this study suggests that perioperative complications can be minimized by initial aggressive medical therapy. If this therapy fails, intraaortic balloon counterpulsation can produce a reduction in perioperative complications similar to that produced by medical therapy.

Surgical treatment for patients with unstable angina pectoris continues to be enthusiastically recommended.[1–7] Several investigators[8–11] consider unstable angina an acute emergency requiring immediate cardiac catheterization and surgery for optimal therapeutic results. However, there are no convincing data to support this approach. It is possible that surgical intervention may be more effective and associated with a lower operative mortality rate and a lower incidence rate of perioperative myocardial infarction if it is preceded by a period of intense medical therapy.

This study was undertaken to evaluate (1) the effect of initial medical therapy and delayed semielective surgery on perioperative complications in patients with unstable angina pectoris, and (2) the effect of intraaortic balloon pumping and urgent coronary surgery on patients with unstable angina who fail to respond to medical therapy.

From the Departments of Internal Medicine (Section of Cardiology) and Surgery (Thoracic and Cardiovascular Division), Yale University School of Medicine, New Haven, Connecticut. This study was supported in part by a Medical Fluid Research Fund grant from Yale University School of Medicine, New Haven, Connecticut. Manuscript received March 28, 1978; revised manuscript received May 30, 1978, accepted May 31, 1978.

Address for reprints: Rene A. Langou, MD, Yale University School of Medicine, Section of Cardiology, 333 Cedar Street, 87 LMP, New Haven, Connecticut 06510.

Materials and Methods

Patients

Cardiac catheterization and coronary arterial bypass grafting were performed in 194 consecutive patients with unstable angina pectoris at Yale-New Haven Hospital from July 1975 through December 1977. These patients were included in the study only after the following criteria for the diagnosis of unstable angina pectoris were satisfied: (1) prolonged typical anginal pain (longer than 20 minutes in duration), (2) typical anginal pain occurring at rest, (3) pain not completely relieved by nitroglycerin, (4) unstable ST-T waves in the electrocardiogram, and (5) failure to document an acute myocardial infarction with serial electrocardiograms and serial enzyme determinations.

Patients responding to medical treatment: After admission to the coronary care unit, all 194 patients were treated medically. The medical management included absolute bed rest, sedation, reassurance and the relief of pain with the administration of narcotic drugs in addition to long- and short-acting nitrates, isosorbide dinitrate, 5 mg sublingually every 3 hours, nitroglycerin tablets sublingually, nitroglycerin ointment, 2 percent (1 to 2 inches [2.5 to 5 cm] every 4 hours) and large oral doses of propranolol.

Sixty-four patients (33 percent) responded to medical therapy within 48 hours after the initiation of full medical therapy in the coronary care unit. All of these patients were free of angina at rest but remained symptomatic with minimal effort. These 64 patients underwent elective cardiac catheterization an average of 12 days (range 6 to 18 days) after admission and elective operation within 2 weeks after cardiac catheterization.

Nonresponders to medical treatment: One hundred thirty patients (67 percent) did not respond to medical therapy and their condition continued to be unstable 48 hours after the initiation of full medical therapy. Of these 130 patients, 75 (58 percent) received intraaortic balloon assistance (Avco Intra-aortic Balloon, Hoffmann-La Roche Inc., Nutley, New Jersey) and underwent emergency cardiac catheterization an average of 2 days (range 1 to 4 days) after the insertion of an intraaortic balloon pump and emergency coronary surgery an average of 2 days (range 0 to 3 days) after cardiac catheterization. Fifty-five of the medical nonresponders (42 percent) did not receive an intraaortic balloon either because the device was not available (48 patients) or because technical difficulties interfered with its placement (7 patients). These 55 patients underwent emergency cardiac catheterization an average of 2.5 days (range 1 to 5 days) after admission and cardiac surgery an average of 2 days (range 0 to 5 days) after cardiac catheterization. Medical therapy was continued up to the day of surgery in medical responders as well as nonresponders. However, in some patients with intraaortic balloon assistance, the total daily dose of propranolol was reduced gradually, and in some patients administration of the drug was completely discontinued before surgery. No recurrence of symptoms was noted in any patient during the withdrawal of propranolol.

Cardiac Catheterization and Coronary Arteriography

These procedures were performed according to standard methods. The single plane right anterior oblique left ventriculogram was analyzed for ejection fraction, regional wall motion and the presence of mitral regurgitation. A coronary arterial lesion of greater than 70 percent luminal obstruction was considered significant. Coronary artery disease was classified as one, two or three vessel disease. Left main coronary artery disease was considered equivalent to two vessel disease.

Intraaortic Balloon Pump

When the intraaortic balloon pump was used, it was introduced through the common femoral artery with an end to side 10 mm Dacron® graft and advanced into the descending thoracic aorta. This procedure was performed under local anesthesia in the surgical intensive care unit. When difficulties were encountered or anticipated, a wire-guided central lumen catheter balloon[12] was introduced under direct fluoroscopy in the cardiac catheterization laboratory. Details of introduction of the balloon and its management have previously been reported.[13] All 75 patients with a preoperative intraaortic balloon used its assistance during the operative procedure up to the time when they were placed on cardiopulmonary bypass. In all 75 patients who received cardiac assistance with an intraaortic balloon pump preoperatively, the balloon was removed within 48 hours after operation.

Coronary Arterial Surgery

Coronary bypass grafts were performed using saphenous vein grafts for the right and left circumflex coronary arteries and, wherever possible, a left internal mammary artery graft was utilized for the left anterior descending coronary artery. A disposable blood oxygenator (Temptrol disposable blood oxygenator, model Q 100, Bentley Laboratories, Inc., Santa Ana, California; or Kolobow disposable membrane oxygenator, Sci-Med., Minneapolis, Minnesota) primed with lactated Ringer's solution was used with moderate hypothermia (28 to 30° C). The left ventricle was vented in all patients by a catheter passed through the right superior pulmonary vein or the ventricular apex into the left ventricular cavity. All blood aspirated into the extracorporeal circuit from the vent or the cardiac suction lines was filtered through a millipore filter before being returned to the oxygenator (Swank-Micro Emboli Filter, Pioneer Filter Co., Beaverton, Oregon). Whole blood was used only if perfusate hematocrit decreased to less than 25 percent. Blood potassium levels were monitored, and additional potassium was added to the oxygenator if the perfusate level decreased to less than 4.0 mEq/liter. When aortocoronary saphenous vein grafts were planned, all proximal anastomoses were constructed with a partially occluding aortic clamp before the institution of cardiopulmonary bypass whenever the patient's condition was stable. Dissection of the left internal mammary artery from the chest wall was accomplished without cardiopulmonary bypass. Distal anastomoses for saphenous vein and internal mammary grafts were performed with the aorta or recipient coronary artery cross-clamped and the heart fibrillating. Each distal anastomosis was probed near its completion to ensure that the anastomotic communication was wider than the grafted coronary artery and hence would not limit blood flow through the system.

Perioperative complications: Myocardial revascularization was considered "incomplete" if grafts were not placed in every diseased coronary branch. Operative mortality was classified as either in-hospital mortality or death up to 6 weeks postoperatively. Perioperative myocardial infarction was diagnosed if serial electrocardiograms revealed evidence of myocardial necrosis within 1 week postoperatively. Serial enzyme determinations were not used as evidence of myocardial infarction because creatinine phosphokinase isoenzyme data were not available in all patients and serum creatinine phosphokinase and glutamic oxaloacetic transaminase levels are elevated by musculoskeletal operative trauma.[14] All patients had a standard 12 lead electrocardiogram recorded

TABLE I

Clinical Characteristics of 194 Patients With Unstable Angina Pectoris

	Patients	
	no.	%
Sex		
Male	154	79
Female	40	21
Previous chronic stable angina	185	95
Remote myocardial infarction	124	64
Congestive heart failure	37	19
Hypertension	68	35
Cardiac enlargement	50	25
Abnormal LVEDP (>12 mm Hg)	89	46
Abnormal LV wall motion	120	62
Abnormal EF (<50%)	84	43
Diseased coronary vessels		
One	22	11
Two	58	30
Three	114	59
LMCD	35	18
Coronary grafts		
One	31	16
Two	84	43
Three or more	79	40
Complete revascularization	89	46

EF = ejection fraction; LMCD = left main coronary artery disease; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure.

TABLE II

Clinical Characteristics of 194 Patients With Unstable Angina Pectoris Classified According to Clinical Groups

	Medical Responders (no.)	Medical Nonresponders With IABP (no.)	Medical Nonresponders Without IABP (no.)	Total (no.)
Sex				
Male	56	50	48	154
Female	17	10	13	40
Previous chronic stable angina	63	60	62	185
Remote myocardial infarction	40	45	39	124
Congestive heart failure	12	14	11	37
Hypertension	19	25	24	68
Cardiac enlargement	17	13	20	50
Abnormal LVEDP (>12 mm Hg)	27	31	31	89
Abnormal LV wall motion	40	37	43	120
Abnormal EF (<50%)	26	28	30	84
Diseased coronary vessels				
One	6	8	8	22
Two	20	18	20	58
Three	35	40	39	114
LMCD	8	14	13	35
Coronary grafts				
One	9	13	9	31
Two	30	25	29	84
Three or more	23	27	29	79
Complete revascularization	27	33	29	89

IABP = intraaortic balloon pumping; other abbreviations as in Table I.

within 24 hours before operation and serial tracings recorded after operation, with the first tracing obtained immediately on arrival in the surgical intensive care unit. The electrocardiographic diagnosis of acute myocardial infarction was based only on the appearance of new pathologic Q waves.[15] The appearance of new intraventricular conduction disorders, increased size of previously present Q waves and S-T segment or T wave changes without new abnormal Q waves were not considered diagnostic of myocardial infarction.

Statistical analysis: A contingency table chi square test was used to examine each of the study factors in relation to the outcome variable (operative mortality or perioperative myocardial infarction). From this analysis the factors associated with each dependent variable could be determined. A difference was considered statistically significant if the probability (P) value was less than 0.05.

Clinical Characteristics

The average age of the patients in this series was 57 years (range 35 to 78); 154 patients (79 percent) were male and 40 (21 percent) female. One hundred eighty-five patients (95 percent) had had chronic stable angina for at least 6 months before inclusion in this study; 124 (64 percent) had evidence of a remote myocardial infarction; 37 (19 percent) had symptoms and signs of congestive heart failure; 68 (35 percent) had hypertension, and 50 (25 percent) had cardiac enlargement on standard chest X-ray film (cardiothoracic ratio greater than 50 percent). The average daily dose of propranolol for the entire group of 194 patients was 380 ± 50 mg (mean ± standard error) after full medical therapy in the coronary care unit. The propranolol dose was rapidly increased until the angina was completely relieved, the patient's resting heart rate was 50 to 55 beats/min or there was clinical evidence that the heart failure could not be controlled with standard therapy.

Eighty-nine patients (46 percent) had abnormal left ventricular end-diastolic pressure (greater than 12 mm Hg); 120 (62 percent) had abnormal left ventricular wall motion in at least one left ventricular segment, and 84 (43 percent) had a depressed ejection fraction (less than 50 percent). Twenty-two patients (11 percent) had one vessel coronary artery disease, 58 (30 percent) two vessel disease, 114 (59 percent) three vessel disease and 35 (18 percent) left main coronary artery disease. The average number of diseased arteries was 2.5 ± 0.7. Thirty-one patients (16 percent) received a single coronary graft, 84 (43 percent) two grafts and 79 (40 percent) three or more grafts. The average number of coronary grafts performed in each patient was 2.4 ± 0.9 (mean ± standard deviation). However, only 89 patients (46 percent) received complete revascularization (Table I). There were no significant differences in clinical, hemodynamic, angiographic and operative factors among medical responders and nonresponders (Table II). However, the daily dose of propranolol was slightly lower in the medical responders (320 ± 40 mg, mean ± standard error) than in the nonresponders (400 ± 80 mg).

Results

Operative mortality: The overall rate of operative mortality for these 194 consecutive patients with unstable angina pectoris was 6.1 percent (12 of 194). There were no deaths among the patients who responded favorably to medical therapy, but the operative mortality rate in patients who did not respond to medical therapy was 9.5 percent (12 of 130); this difference was statistically significant (P <0.05). Medical nonresponders with intraaortic balloon pumping preoperatively had a significantly lower rate of operative mortality (5.3 percent, 4 of 75) than those without balloon pumping

TABLE III

Operative Mortality and Incidence of Perioperative Myocardial Infarction in 194 Patients With Unstable Angina

	no. of Cases	Deaths		Perioperative Myocardial Infarction	
		no.	%	no.	%
Medical responders	64	0	0	4	6
Medical nonresponders	130	12	9.2	21	16
With IABP	75	4	5.3	5	6.6
Without IABP	55	8	14.5	16	29
Overall	194	12	6.1	25	13

IABP = intraaortic balloon pumping.

(14.5 percent, 8 of 55) ($P < 0.05$). However, the operative mortality rate of medical nonresponders with preoperative balloon pumping was higher (5.3 percent, 4 of 75) than the rate of patients who responded to medical therapy (0 percent, 0 of 64), but the difference was not statistically significant (Table III).

Analysis of other probable preoperative or operative risk factors for operative mortality using contingency table chi square analysis revealed that operative mortality rate was not related to clinical, hemodynamic, angiographic or operative factors (age, sex, previous chronic stable angina, remote myocardial infarction, congestive heart failure, hypertension, cardiac enlargement, abnormal left ventricular end-diastolic pressure, abnormal left ventricular wall motion, abnormal left ventricular ejection fraction, number or degree of diseased coronary vessels, number of aortocoronary bypass grafts or completeness of revascularization) in the three groups of patients (medical responders and medical nonresponders with and without intraaortic balloon pumping).

Perioperative myocardial infarction: The overall incidence rate of perioperative myocardial infarction in all patients was 13 percent (25 of 194). The rate in patients who responded to medical therapy was 6 percent (4 of 64) and in nonresponders 16 percent (21 of 130) ($P < 0.05$). Nonresponders with preoperative intraaortic balloon pumping had a significantly lower incidence rate of perioperative myocardial infarction (6.6 percent, 5 of 75) than those without balloon pumping (29 percent, 16 of 55) ($P < 0.001$). The difference in incidence rate of perioperative myocardial infarction in medical responders (6 percent, 4 of 64) and nonresponders with intraaortic balloon pumping (6.6 percent, 5 of 75) was not significant (Table IV).

Analysis of probable risk factors for perioperative myocardial infarction showed that myocardial infarction was not related to any other variable present in each clinical group. The perioperative myocardial infarction was located in the anterior wall in 8 patients, the inferior wall in 14 patients and the anterolateral wall in 3 patients. Electrocardiographic signs of a perioperative myocardial infarction appeared within the first 24 hours postoperatively in 18 patients and within 72 hours postoperatively in all patients studied.

Discussion

Patients were included in this study only if they met rigid diagnostic requirements and if they underwent diagnostic cardiac catheterization and coronary arterial surgery during the same hospital admission. We estimate that the number of patients excluded from the study because they failed to meet our criteria was as large as the number of patients reported on. Our definition of the syndrome of unstable angina corresponds to the one discussed by Hultgren[10] and identified as "type II, or angina at rest, or acute coronary insufficiency." Because of our strict criteria for selection, our patients constitute a relatively homogeneous clinical group.

In this study, the patients were classified into two groups according to their response to medical therapy 48 hours after the initiation of full therapy in the coronary care unit. Thirty-three percent (64 of 194) of the patients with unstable angina responded promptly to medical therapy, but 75 percent (130 of 194) continued to have angina pectoris at rest despite full medical therapy. Previous reports[16–18] have indicated that the condition of some patients with unstable angina pectoris can be controlled effectively with medical therapy.

Operative mortality: The overall rate of operative mortality in this study of patients with unstable angina was 6.1 percent, which is comparable with the rate reported by our group[19] in a previous study as well as the rate reported from several medical centers.[1–6,20] There were no operative deaths among the patients who responded to medical therapy and then underwent elective cardiac catheterization and surgery. Our published retrospective study[19] including patients treated at our institution from January 1974 to July 1975 suggested that the response to medical therapy was one of the factors determining operative mortality. The present prospective study confirms this finding. However, it does not answer the critical question of whether surgery improves the rate of survival or prevents myocardial infarction.

The operative mortality rate in patients whose anginal symptoms were not controlled with medical therapy was 9.2 percent, a rate significantly higher than that of patients responding to medical therapy. However, those patients receiving preoperative intraaortic balloon assistance had a lower operative mortality rate (5.3 percent) than that of patients who did not receive balloon assistance (14.5 percent). An intraaortic balloon pump was inserted in patients who did not respond to medical therapy if an intraaortic balloon pump console was available and if the presence of severe peripheral vascular disease did not totally preclude passage of an intraaortic balloon catheter.

Analysis of the distribution of all probable preoperative and operative risk factors for operative mortality with a contingency table chi square test disclosed no significant differences among the three clinical groups (medical responders and medical nonresponders with and without intraaortic balloon pumping).

Perioperative myocardial infarction: The reported incidence[20,21] of perioperative myocardial in-

farction is sufficiently great to offset the overall results of coronary bypass grafting in patients with unstable angina. The overall incidence rate of perioperative myocardial infarction in this study was 13 percent, a rate similar to that reported from other large medical centers.[20]

Our medical responders had a perioperative myocardial infarction rate of 6 percent, which was significantly lower than the 16 percent rate in medical nonresponders. If medical nonresponders had intraaortic balloon pumping preoperatively, their perioperative myocardial infarction rate was not different from the rate of medical responders. The distribution of all probable risk factors for perioperative myocardial infarction among the three clinical groups was closely comparable according to contingency table chi square analysis. Therefore, we believe that perioperative myocardial infarction in patients with unstable angina undergoing coronary surgery may be significantly minimized with initial successful medical therapy followed by elective cardiac catheterization and surgery. If medical therapy fails, preoperative cardiac assistance with an intraaortic balloon pump may produce a decrease in the rate of perioperative myocardial infarction almost identical to the decrease produced with medical therapy.

Clinical implications: The preliminary results from the national randomized study for unstable angina pectoris[20] indicate that the rates of in-hospital mortality in the medical and surgical groups are almost equal (medical 6 percent and surgical 5 percent). The rate of early incidence of myocardial infarction is higher in the surgical group (because of a perioperative myocardial infarction rate of 17 percent), and the incidence rate of angina pectoris in the late follow-up period is higher in the medical group. Our study is not designed to determine whether medical or surgical therapy is superior for patients with unstable angina pectoris but rather to identify the best approach for patients with angina pectoris for whom surgical therapy is selected.

The following conclusions are the result of our experience in surgically treating a selected group of 194 patients with unstable angina pectoris from July 1975 through December 1977: (1) the condition of a large number of patients with unstable angina pectoris can be controlled with aggressive medical therapy; (2) patients who respond to medical therapy have a low rate of operative mortality and a low incidence rate of perioperative myocardial infarction; and (3) if medical therapy fails to control unstable angina pectoris, intraaortic balloon pumping minimizes the risks of coronary surgery (operative mortality[22] and perioperative infarction).

It is attractive to hypothesize that if the operative mortality rate and the rate of perioperative myocardial infarction are diminished, surgery is the most appropriate therapy for unstable angina pectoris. Although our results demonstrate that the combination of initial aggressive medical therapy and the preoperative insertion of an intraaortic balloon pump decreases the rate of both operative mortality and perioperative myocardial infarction, we cannot conclude from this study that surgical therapy is preferable to medical therapy in patients with unstable angina.

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Unstable Angina: The Case for Operation

GORDON N. OLINGER, MD, FACC
LAWRENCE I. BONCHEK, MD, FACC
MICHAEL H. KEELAN, Jr., MD
DONALD D. TRESCH, MD, FACC
RONALD SIEGEL, MD
VIRINDERJIT BAMRAH, MD
FELIX E. TRISTANI, MD, FACC

Milwaukee, Wisconsin

From July 1975 through September 1977, surgical revascularization was performed in 95 consecutive patients with unstable angina, 53 at high risk (defined as in-hospital pain at rest with reversible ischemic electrocardiographic changes) and 42 at low risk (defined as pain at rest remitting upon hospitalization). Historical, electrocardiographic and cardiac catheterization data were similar in both groups; however, patients at high risk required large doses of propranolol, and one patient needed additional intraaortic counterpulsation for preoperative stabilization of ischemia. Proximal left anterior descending (79 patients) and left main (15 patients) coronary artery disease with abnormal ventricular function characterized both groups of patients with unstable angina. Revascularization (2.5 grafts/patient) was performed with hypothermia and intermittent ischemic arrest. Complications included one death and three perioperative infarctions. No patient needed inotropic support. No late deaths occurred in a follow-up period of up to 30 months. The data indicate that (1) "prophylactic" preoperative intraaortic balloon counterpulsation in patients with unstable angina, although advocated by some surgeons, is unnecessary; (2) the very small incidence of complications when unstable angina—particularly high risk unstable angina—is managed as outlined strongly suggests that surgical revascularization is definitive therapy; and (3) the therapeutic implications of large scale controlled studies of medical versus surgical therapy for unstable angina, which include results achieved 3 or 4 years ago and describe significantly higher rates of mortality and infarction than those reported here and by others, may not be pertinent to therapeutic decisions made today.

The role of surgical revascularization in the management of unstable angina remains clouded by several issues. First is the definition of unstable angina. It is well recognized that patients with so-called acute coronary insufficiency, intermediate coronary syndrome, accelerated or crescendo angina or unstable angina comprise a heterogeneous group encompassing various risk factors. Yet, despite recent reports[1–3] that provide a clear and unequivocal definition of unstable angina, the term is still used loosely. Analysis of several current reports[4–11] on unstable angina is difficult because the lack of rigid criteria for unstable angina makes it likely that dissimilar populations are being examined. Implicit in all definitions is the attempt to identify a "high risk" category indicating increased propensity to acute infarction and early mortality.[12] Contemporary medical management with aggressive beta adrenergic blockade as its cornerstone has permitted in-hospital stabilization of acute ischemic syndromes and thereby has provided a more favorable environment for operation and its attendant risks.[13,14] In this sense, more successful medical therapy of unstable angina has increased the need to define the term rigorously.

From the Department of Thoracic and Cardiovascular Surgery and Section of Cardiology, The Medical College of Wisconsin, Milwaukee County Medical Complex, and Wood Veterans Administration Center, Milwaukee, Wisconsin. Manuscript received November 28, 1977; revised manuscript received May 23, 1978, accepted May 24, 1978.

Address for reprints: Gordon N. Olinger, MD, Department of Thoracic and Cardiovascular Surgery, The Medical College of Wisconsin, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226.

The second issue relates to the results of medical versus surgical therapy. It has been generally, although not universally, accepted that in patients with unstable angina operation will result in more perioperative complications—death, myocardial infarction and depression of myocardial performance—than occur in patients undergoing purely elective revascularization. Numerous groups[4–6,8–10,13,15–21] have reported a greater incidence of such ischemic complications from surgery for "unstable angina." The early results from a recently reported prospective cooperative study[22,23] of medical versus surgical therapy for unstable angina support the contention that ischemic complications from both modes of treatment may be similar. Other reports[7,24–28] and our own results suggest otherwise. Although our uncontrolled series cannot attempt to refute the efficacy of medical therapy alone for unstable angina, it does set into proper context the kind of results to be expected with surgery today.

The third issue relates to perioperative management. Cardiac support techniques are now being used by some surgeons to increase the margin of coronary reserve in the patient with unstable angina and thereby reduce perioperative ischemic morbidity. The technique used most widely has been preoperative intraaortic balloon counterpulsation.[15,24,25,29] However, this procedure is not without risk and, although it may help some patients, it may cause unnecessary complications in others.

This report reemphasizes a rigorous definition of unstable angina in the current context of medical therapy. It demonstrates that in an unselected consecutive series of patients with unstable angina managed with aggressive supportive medical therapy combined with careful attention to perioperative myocardial protection and to anesthesia techniques, surgical revascularization can be accomplished with a very low level of morbidity, similar to that for elective revascularization. It also demonstrates that in the large majority of patients the routine application of intraaortic balloon counterpulsation is unnecessary to achieve such results.

Materials and Methods

Patients: Between July 1975 and September 1977 at the Milwaukee County Medical Center and between July 1976 and September 1977 at the Wood Veterans Administration Hospital (the periods encompassing the surgeons' experience at the Medical College of Wisconsin), 95 patients underwent coronary revascularization for unstable angina. Fifty-three patients were admitted to the coronary care unit with angina at rest that was progressive in frequency or severity, or both; while in the hospital receiving medical therapy these patients had additional episodes of angina at rest. Twenty-eight of these 53 patients had angina of recent onset (less than 3 months), and 25 had a change in the pattern of chronic angina. The longest duration of pain at rest ranged from 15 to 300 minutes (average 50). Angina in each patient was associated with reversible ischemic electrocardiographic changes consisting of either ST-T changes or, occasionally, ventricular ectopy requiring parenteral antiarrhythmic drug therapy. Serial determinations of serum cardiac enzyme levels (creatine kinase, serum glutamic oxaloacetic transaminase and lactic dehydrogenase) failed to demonstrate ischemic myocardial damage. This group of 53 patients was considered to have "high risk" unstable angina according to criteria previously reported.[12,18,26] Forty-two additional patients were admitted to the coronary care unit with a history of angina that progressed in frequency or severity, or both. Although many of these patients had had prolonged episodes of pain suggestive of possible myocardial infarction, none continued to have pain in the hospital, and none had significant serum enzyme changes. This group of 42 patients was considered to have "low risk" unstable angina.

Medical treatment: Upon admission to the hospital, all patients with high risk angina were treated with progressive doses of propranolol unless this drug was contraindicated by obstructive pulmonary disease. Nitrates, antihypertensive agents and antiarrhythmic agents were used when indicated. Pharmacologic stabilization of acute ischemic symptoms was attempted in all patients before cardiac catheterization and operation. Propranolol relieved the symptoms of 56 percent of the patients at high risk, and they had no further pain before operation. Forty-four percent of patients still had intermittent pain at rest up to the time of operation, but only one of these patients required preoperative, post-catheterization intraaortic balloon counterpulsation because of unremitting pain totally refractory to medical management. Precatheterization balloon counterpulsation was not required in this series.

Cardiac catheterization: The time interval from admission to catheterization and operation tended to vary inversely with the ability to control ischemia with medical therapy. In patients at high risk the time to catheterization averaged 5 days (range 1 to 14) and that to operation averaged 9 days (range 1 to 60). Very precarious coronary anatomy was a factor that hastened operative intervention after catheterization was completed, provided beta adrenergic blockade was considered optimal. Patients at low risk underwent catheterization an average of 5 days (range 1 to 15) and operation an average of 12 days (range 2 to 35) after admission.

Cardiac catheterization consisted of measurement of right and left heart hemodynamic variables, left ventriculography in the right and left anterior oblique projections and coronary angiography with either the Sones or Judkins technique. Left ventricular ejection fraction was calculated from the right anterior oblique projection.

Coronary revascularization: This was performed under balanced anesthesia with particular attention directed to gradual induction of narcosis, avoiding hypotension or hypertension. When hypertension did occur, it was treated promptly with nitroprusside. Cardiopulmonary bypass was carried out with moderate hemodilution (hematocrit maintained above 26 percent), moderate systemic hypothermia (30° C) and a mean aortic perfusion pressure greater than 70 mm Hg. Distal saphenous vein anastomoses were performed during intermittent periods of 8 to 15 minutes of ischemic arrest. Each proximal anastomosis was performed after its respective distal anastomosis by placing a side-biting clamp on the ascending aorta, thus allowing a period of coronary reperfusion in the beating heart at least as long as the preceding ischemic period. Left ventricular venting was used at the discretion of the operating surgeon and was always used when there was incomplete collapse of the pulmonary artery, distension of the left ventricle or recurrent ventricular fibrillation due to hypothermia.

Postoperatively, particular care was again directed toward avoiding hypertension (systolic pressure greater than 150 mm Hg), which when present was treated with intravenous chlorpromazine, nitroprusside or trimethaphan. Serial elec-

TABLE I

Historical Data in 95 Patients

	High Risk (53 patients)		Low Risk (42 patients)	
	no.	%	no.	%
Myocardial infarction	20	38	20	48
Heart failure	3	6	2	5
Ventricular arrhythmias	11	21	6	14
Hypertension	29	55	19	45
Diabetes mellitus	10	19	6	14
Hyperlipidemia	12	23	9	21
Smoking	38	72	28	67

trocardiograms and serum enzyme determinations (creatine kinase, serum glutamic oxaloacetic transaminase and lactic dehydrogenase) were obtained daily for 3 days and again before discharge. Postoperative infarction was defined as the appearance of new, persistent Q waves with a duration of 0.03 second or longer.

All patients were followed up by the cardiology faculty at the Milwaukee County Medical Center and Wood Veterans Administration Hospital. Follow-up on all patients was continued through February 1978.

Results

Clinical data: In the group of patients at high risk there were 39 men and 14 women; the average age was 57 years (range 34 to 76). In the group at low risk there were 34 men and 8 women; the average age was 55 years (range 38 to 74). The distribution of risk factors for coronary disease and historical documentation of previous cardiac ischemic damage was similar in both groups (Table I). Although 42 percent of all patients had a history of previous myocardial infarction, only 5 percent had a history of clinical heart failure. There was an 18 percent incidence rate of significant ventricular arrhythmias requiring oral antiarrhythmic therapy. No correlation was noted between arrhythmias and a history of infarction. Half of the patients had a history of hypertension, the majority smoked and about one fifth had either diabetes or documented hyperlipidemia, or both.

Ventricular function: Cardiac catheterization revealed some abnormality of ventricular function in the majority of patients (Table II). Elevated left ventricular diastolic filling pressure was present at rest in 36 percent of the high risk and 26 percent of the low risk group, and the cardiac index at rest was less than normal in 25 percent and 14 percent of patients in these groups, respectively. Ventricular ejection fraction was less than normal (0.55) in half of the patients at high risk and one fourth of those at low risk but was less than 0.35 in only one patient. Some abnormality of ventricular segmental wall motion was found in 61 percent of the series in approximately equal distribution in the two groups.

Angiographic findings: Coronary angiography demonstrated a distribution of lesions typical of that previously reported for patients with unstable angina.[6,22] Left main coronary stenosis greater than 50 percent was present in 16 percent of the 95 patients, 10 at high risk and 5 at low risk. Significant occlusive disease (greater than 70 percent narrowing of cross-sectional diameter) was present in the left anterior descending coronary artery in 83 percent of patients. In the high risk group, 39 patients had stenosis and 4 had occlusion of the left anterior descending coronary artery; in the low risk group, 27 patients had stenosis and 9 had occlusion of this vessel. Significant diagonal branch disease was present in 17 patients at high risk and 13 at low risk. Significant lesions of the left circumflex and right coronary arteries tended to be less preponderant than lesions of the left anterior descending artery and

TABLE II

Ventricular Function in 95 Patients*

	High Risk (53 patients)			Low Risk (42 patients)		
	Average	no.	%	Average	no.	%
LV end-diastolic pressure (mm Hg)	13.8			12.6		
<15		33	62		30	71
>15		19	36		11	26
Cardiac index (liters/min per m^2)	3.1			3.0		
>2.5		36	68		33	79
<2.5		13	25		6	14
LV ejection fraction	0.61			0.66		
>0.55		21	40		26	62
>0.44 <0.55		19	36		7	17
>0.34 <0.44		6	11		2	5
<0.35		1	2		0	0
LV segmental motion						
Normal		20	38		15	36
Focal hypokinesia or akinesia		25	47		25	60
Diffuse hypokinesia		6	11		2	4

* Differences in total reflect that not all patients had complete hemodynamic or ventriculographic studies.
LV = left ventricular.

were distributed equally in the two groups of patients. In summary, single vessel disease (in the left anterior descending coronary system in all) was present in 10 patients at high risk and 9 at low risk, double vessel disease in 16 patients at high risk and 11 at low risk, and triple vessel disease in 27 patients at high risk and 22 at low risk. Including the left main coronary artery and the three major vessels, in addition to the major diagonal, circumflex marginal and right posterior descending branches, there were 254 significant lesions in the total group with an average of 2.7 lesions/patient.

Preoperative medical management: Despite the apparent hemodynamic and anatomic similarity of patients in the high and low risk groups, their in-hospital clinical courses required different medical regimens before operation. Forty-nine of the 53 patients at high risk received propranolol (the other 4 patients had severe obstructive pulmonary disease contraindicating beta adrenergic blockade). The average daily dose was 128 mg, and 18 patients received more than 160 mg daily. In patients whose clinical state had been stabilized, the dose of propranolol was tapered to one half of the daily dose 12 hours before operation. The drug was continued at full dose in patients who continued to have intermittent angina. In contrast, only 29 of the 42 patients at low risk were taking propranolol in the immediate preoperative period, and only 5 received 160 mg or more daily. The average daily dose for the low risk group was 91 mg. This difference in average dose was significant ($P < 0.05$).

Surgical procedures and results: At operation, complete revascularization was accomplished in nearly every patient; 242 bypass procedures were performed, all but 12 with vein grafts. There were 13 single, 35 double, 29 triple and 18 quadruple graft procedures. Eight of the 12 internal mammary artery grafts were placed in the low risk group. The average number of grafts per patient was 2.5 in the high risk and 2.6 in the low risk group.

Perioperative mortality and morbidity were low in both groups (Table III). The one death occurred in a 71 year old woman with high risk unstable angina who was recovering uneventfully from a double bypass graft when, on the 3rd postoperative day, she received a mismatched transfusion for a low hematocrit, sustained a severe transfusion reaction and died from subsequent multisystem deterioration.

There were three cases of perioperative myocardial infarction (defined as the occurrence of persistent new Q waves in the serial electrocardiogram). The first occurred in a patient at high risk who had had chest pain with systolic blood pressure as high as 180 mm Hg on the afternoon after catheterization. His unremitting pain required narcotic drugs for even partial relief, and at emergency operation the anteroapical region of the left ventricle was found to be and cyanotic dyskinetic. Postoperatively, the electrocardiogram showed evolution of an acute anterior wall infarct despite vein grafts to both stenotic vessels. His postoperative convalescence was otherwise unremarkable, and subsequent catheterization revealed patent grafts. The second infarction occurred in a patient with low risk angina and severe triple vessel disease. A vein graft was attempted to a small and diseased circumflex marginal artery; technical difficulties with the distal anastomosis prompted ligation of this small vessel. The patient's electrocardiogram showed evolution of a lateral wall infarction, but otherwise she had an uncomplicated course. The third infarction occurred in the intensive care unit in a patient at low risk who manifested electrocardiographic changes of an inferior wall infarction and with these a transient bradyarrhythmia after revascularization of the left anterior descending coronary artery and diagonal branch. The patient had no significant stenosis in a dominant right coronary artery that had shown severe spasm during catheterization. Recatheterization before discharge revealed a patent right coronary artery, patent left coronary grafts and no remarkable abnormality of ventricular contraction. Thus, of the three infarctions one had undoubtedly been developing preoperatively, one was a consequence of operation and one may have been due to severe coronary spasm.

TABLE III

Postoperative Results in 95 Patients

	High Risk (53 patients) (no.)	Low Risk (42 patients) (no.)	Total (95 patients) no.	Total (95 patients) %
Death	1	0	1	1
Infarction	1	2	3	3
Inotropic support	0	0	0	0
IABC	1	0	1	1
Nitroprusside therapy	24	26	52	55
Atrial arrhythmia	9	9	18	19
Ventricular arrhythmia	12	2	14	15

IABC = intraaortic balloon counterpulsation.

Postoperative complications: There was a distinct absence of need for postoperative cardiotonic pharmacologic or mechanical ventricular support. *None of the 95 patients required positive inotropic drugs at any time in the postoperative period.* Indeed, the most consistent postoperative problem was the presence of systolic hypertension requiring intravenous vasodilator for control. Nitroprusside, less commonly trimethaphan, was administered to 24 patients with high risk and 26 with low risk angina. The single patient who required postoperative intraaortic balloon counterpulsation was a 67 year old woman with high risk unstable angina and diffuse coronary artery disease. Technical considerations precluded complete revascularization of her functionally depressed left ventricle. Upon cessation of cardiopulmonary bypass, she had severe hypertension with a systolic blood pressure exceeding 200 mm Hg. Nitroprusside therapy could not be instituted without recurrent episodes of sudden vasodilatation, hypotension and electrocardiographic evidence of ischemia. An intraaortic balloon was placed electively and successfully to assist in systolic unloading and to prevent the profound loss of diastolic coronary perfusion pressure

that occurred with nitroprusside infusion alone. The patient was weaned from counterpulsation over a period of 24 hours but required nitroprusside for an additional 24 hours before her hypertension came under control.

Postoperative ventricular arrhythmias, consisting of frequent premature ventricular complexes, were noted in 14 patients; the arrhythmias had been present in 10 of the patients preoperatively. Ventricular ectopy was treated with intravenous lidocaine and, when necessary, procainamide or quinidine. In four patients preoperative ventricular ectopy was controlled with revascularization alone.

Late results: The long-term follow-up periods of the patients studied range from 5 to 30 months (average 15.9). Complete follow-up information was obtained in 92 (98 percent) of the 94 operative survivors, with 2 patients lost to follow-up. There have been no late deaths. New late postoperative myocardial infarcts have been documented in five patients (5.3 percent), two in the high risk and three in the low risk group. Infarction occurred from 6 to 12 weeks postoperatively in three patients and, on the basis of findings at recatheterization, could be attributed to graft occlusion in each instance. The fourth infarction occurred at 11 months in a patient who has not been restudied. The fifth occurred at 15 months in a coronary distribution remote from the patient's two grafts, both of which are patent.

Symptomatic relief of unstable angina was achieved in every patient. Fifty patients (54 percent) have had complete relief of angina. Seventy-six patients (83 percent) have returned to work (41 patients) or are actively retired (35 patients). Twelve patients describe themselves as being inactively retired, and only four patients are disabled, two with noncardiac disability and one with major psychoneurotic disability. Twenty-four patients have undergone late postoperative cardiac catheterization (average postoperative interval 7 months, range 1 to 17), some for evaluation of persistent cardiac symptoms and others as a part of routine follow-up. These 24 patients had 56 bypass grafts, 48 of which were patent for a late patency rate of 86 percent in this small and adversely selected group of patients.

Discussion

The results of coronary revascularization in this consecutive unselected series of patients with unstable angina demonstrate that surgical therapy for this condition can be accomplished safely, with minimal ischemic morbidity and excellent relief of symptoms. These results reaffirm previous reports on similar series of patients suggesting that the risk of surgical revascularization in the patient with unstable angina can be as small as the current risk of elective revascularization.[7,24–28]

Importance of vigorous medical treatment: Our series further supports the concept of initial medical control with aggressive beta adrenergic blockade,[14] treatment of ventricular ectopy and control of hypertension. The large majority of patients with unstable angina managed in this fashion can undergo cardiac catheterization and surgery after deliberate review of the clinical course to rule out acute myocardial infarction and the hemodynamic and angiographic data from catheterization. In most instances, operation is performed on a semielective basis with regular anesthesia and nursing and operating personnel. Administration of propranolol is continued up to the time of operation to maintain a stable catecholamine milieu and to facilitate safe induction of anesthesia. Because we observed uniformly excellent hemodynamic responses to revascularization without a need for postoperative positive inotropic pharmacologic support, we do not advise that propranolol should necessarily be tapered preoperatively.

Control of postoperative hypertension: In conjunction with the lack of need for postoperative cardiotonic support, we were impressed by the large incidence of postoperative hypertension, commonly found in patients with low left ventricular filling pressure. These patients usually respond in several hours to vasodilatation induced by nitroprusside combined with gradual volume expansion, but on occasion they require prolonged use of nitroprusside or trimethaphan, or both. We believe that control of hypertension is crucial to prevent complications at aortic anastomosis and cannulation sites and, in some patients, to preclude the development of regional ischemia in incompletely revascularized myocardium. In the one circumstance in this series in which postoperative intraaortic balloon counterpulsation was used, immediate postcardiopulmonary bypass hypertension was associated with incomplete revascularization. Counterpulsation was used to assist systolic unloading and to augment diastolic blood pressure that otherwise decreased precipitously with pharmacologic vasodilatation.

Preoperative intraaortic balloon counterpulsation: This was used only once, when prolonged episodes of ischemia refractory to beta adrenergic blockade and coronary vasodilators necessitated the administration of narcotic drugs for relief of pain. Counterpulsation can immediately reverse discrepancies between oxygen supply and demand and rapidly reverse ischemic symptoms. *In this particular setting* counterpulsation may prevent many of the perioperative myocardial infarcts that would otherwise occur. The results obtained using intraaortic balloon counterpulsation more routinely for unstable angina[24,25] tend to support this viewpoint. One of the three infarcts in our series probably began preoperatively in a man with progression of ischemia unremitting with morphine and nitroglycerin. If a patient with similar clinical symptoms presented to our service today counterpulsation would be instituted immediately. This recommendation of limited use of intraaortic balloon counterpulsation is a less aggressive approach than that of some authors,[25,29] but we are concerned about the morbidity associated with balloon pumping and wish to avoid any unnecessary vascular complications in patients who can be managed safely without it. Furthermore, the small incidence of myocardial infarction in this series confirms our view that routine preoperative counterpulsation is unwarranted.

High risk versus low risk unstable angina: This report has dealt with two groups of patients with unstable angina. Patients in the low risk group have what has often been called accelerated, crescendo or progressive angina, but such patients have been included in many series of patients with unstable angina. Ischemic symptoms abated immediately when these patients were placed in a controlled hospital environment. The high risk group consists of patients who have similar out-of-hospital pain as well as ischemic symptoms within a controlled hospital environment. Although there was clearly a spectrum of instability or, more appropriately, of coronary vasodilator reserve in such patients, extending from early control with bed rest and small dose beta blockade to a requirement for progressive beta blockade and in one patient balloon counterpulsation, this group as a whole corresponds to the high risk group of patients with unstable angina delineated by us and by others.[12–14,16,18,20,22,24,26–28] Our series of patients with high and low risk angina indicates no clear-cut factors discriminating the two groups other than clinical course. This is consistent with the data from the prospective randomized study of Bertolasi et al.[6] showing the natural history of medically treated "intermediate angina" (high risk) to be far worse than that of "progressive angina" (low risk), with an average 32 month mortality rate of 46 versus 7 percent and an infarct rate of 38 versus 7 percent, respectively.

We believe that the clinical course is an important indicator of risk and recommend that in the future the term unstable angina be used *only* for patients with continued evidence of ischemia in a controlled hospital environment. Contemporary beta blockade therapy results in essentially stable clinical condition in the majority of patients who several years ago would have had recurrent prolonged episodes of ischemia necessitating hastily performed catheterization and emergency operation. In 1978, very few patients remain in truly unstable status when propranolol dosage is 240 or more mg daily, and the condition of even these patients can be stabilized with intraaortic balloon counterpulsation. Thus unstable angina connotes a dynamic clinical syndrome requiring careful coordination of medical and surgical services for optimal individual therapy.

Surgical implications in light of recent large scale cooperative studies: Although we believe that our series of patients with high risk angina is representative and valid for comparison with other series based on a similar classification of patients, an important question is: In the climate of cooperative, controlled studies of medical versus surgical therapy for unstable angina, what is the merit of presenting another isolated surgical series as justification for surgical therapy? In his recent carefully considered comments on unstable angina and the National Institutes of Health cooperative study, Scheidt[30] concludes that the operative mortality rate (5 percent) and perioperative myocardial infarction rate (18 percent) in that study are reasonable on the basis of available statistics on current results of elective myocardial revascularization. We believe that such mortality and morbidity statistics are not optimal, especially for elective myocardial revascularization but also for revascularization in patients with unstable angina. Although every effort is made in cooperative studies to control patient input variables, one set of variables in surgically treated patients that has not been rigorously controlled is the technique of coronary revascularization and, specifically, the means of protecting the myocardium from ischemic injury before, during and immediately after cardiopulmonary bypass.[26] Even the conduct of cardiopulmonary bypass itself may differ from institution to institution and at the same institution from surgeon to surgeon.

The issue of myocardial protection is perhaps the most urgent in the field of cardiac surgery today. It is well recognized that a great part of the "unexplainable" ischemic damage previously seen during cardiac operations may be avoided with certain techniques but provoked by other techniques still used by many surgeons. The patient with unstable angina has the lowest threshold for iatrogenic ischemic injury because of his lack of coronary vasodilator reserve and the precariousness of balance between myocardial oxygen supply and demand. The failure to standardize surgical techniques, report the techniques used, correlate them with the results achieved and document the incidence of postoperative myocardial depression (most noticeable by the need for postoperative inotropic support) renders the results of large scale studies difficult to interpret and subject to skepticism. This is especially true of cooperative studies because it is inappropriate to report the results by institution. We are not aware of any medical series of patients with high risk unstable angina that has results comparable with the optimal results of surgical therapy. The only death in our own group of surgically treated 53 patients at high risk was due to a clerical error.

With the aggressive support of their medical colleagues, modern cardiac surgeons have at their disposal a variety of means of reducing the perioperative risk of ischemic complications of myocardial revascularization. With appropriate care of the heart in the operating room, every patient with acute coronary ischemia who does not already have acute muscle damage and whose coronary vasculature is suitable for revascularization is potentially able to have safe and highly effective surgical treatment of his disease. This is not meant as an enthusiastic claim for the supremacy of surgical therapy but as a statement attesting to the consistent improvements being made in the surgical treatment of coronary disease. It is also meant to demonstrate that reviews of the literature and controlled studies of medical versus surgical treatment that include surgical results achieved 3 or 4 years ago and that describe higher surgical mortality and infarction rates than those reported here may not be pertinent to therapeutic decisions made today.

Acknowledgment

We are grateful to Wayne Swart and Jay Stemper for their contributions in the preparation of this manuscript.

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Congenital Heart Disease in a Cohort of 19,502 Births With Long-Term Follow-Up

JULIEN I. E. HOFFMAN, MD, FACC
ROBERTA CHRISTIANSON, MA

San Francisco and Berkeley, California

The Child Health and Development Studies are longitudinal studies of pregnancy and the normal and abnormal development of the offspring. Women who were members of the Kaiser Foundation Health Plan entered the study in early pregnancy, and their children were examined frequently until the youngest child in the study was 5 years old. This is a more intensive follow-up than hitherto reported.

Of the 19,044 live-born children, 163 had definite and another 31 had possible congenital heart disease; the crude incidence rates per 1,000 live births were 8.8 for definite congenital heart disease and 10.4 for definite plus possible congenital heart disease. The incidence rate of congenital heart disease was 7.9 percent among all stillborn fetuses subjected to autopsy and 10.2 percent among those in this group with autopsies evaluated as being detailed enough to detect heart disease. Among the live-born children with congenital heart disease, 21 died in the neonatal period and 22 died in later infancy and childhood; about half the deaths were judged to have been due to heart disease. About 30 percent of the children with congenital heart disease had associated severe anomalies of other systems. In the whole cohort, 50 children had diagnosed chromosomal abnormalities (2.63/1,000 live births) and about 30 percent of them had congenital heart disease. Among the group of 163 children with definite congenital heart disease, the diagnosis was made in 46 percent by age 1 week, in 88.3 percent by age 1 year and in 98.8 percent by age 4 years.

Studies of the incidence of congenital heart disease in populations provide markedly different incidence rates; the more intensive studies have shown high values of 8 to 9/1,000 live births.[1,2] Some low rates have come from studies that followed up children for only a short time after birth, used survey methods better adapted to detecting survivors than infants who died early or relied on casual reporting of patients with congenital heart disease to a registry. The higher rates were from longitudinal studies that attempted to identify all children with congenital heart disease in a cohort of births. However, even these studies have imperfections. Because the initial diagnosis of congenital heart disease is usually made by a physician who is not a cardiologist, minimal lesions may be missed. Little attempt has been made in any study to determine the frequency of false negative diagnoses. Furthermore, the accuracy of diagnosis of minimal lesions has not been well evaluated. The multiple observations obtained in our long-term study acted to minimize these errors.

Another potential source of error in determining the incidence of congenital heart disease is failure to evaluate stillborn fetuses who are reported to have a high rate of congenital heart disease.[1] Because this group also has a high proportion of complex lesions, failure to evaluate the group might vitiate attempts to define etiologic associations.

From the Child Health and Development Studies, School of Public Health, University of California, Berkeley, and the Cardiovascular Research Institute and Department of Pediatrics, University of California, San Francisco. This study was supported by Grant HD 07256 of the National Institute of Child Health and Human Development of the National Institutes of Health, Bethesda, Maryland. Manuscript received January 30, 1978; revised manuscript received May 24, 1978, accepted May 24, 1978.

Address for reprints: Roberta Christianson, Child Health and Development Studies, 3867 Howe Street, Oakland, California 94611.

We now report a study of a large cohort of births in the San Francisco-East Bay region. The design of the study allowed information to be obtained from stillborn fetuses, and the long duration of follow-up and high frequency of examinations provided excellent opportunities for ascertainment and evaluation of congenital heart disease.

Material and Methods

Case Material

The data were collected within the framework of the Child Health and Development Studies, whose objectives are to investigate the relations of biologic, medical and environmental factors in parents—including events in pregnancy, labor and delivery—to the normal and abnormal development of offspring. A detailed description of these studies and a first analysis of the data on congenital heart disease have been reported[3]; the following is a brief outline of the procedures.

The Child Health and Development Studies were conducted among members of the Kaiser Foundation Health Plan, a prepaid medical care program in the San Francisco-East Bay region, with services furnished by a tightly organized group of obstetricians, pediatricians and other specialists. Subscribers to the Health Plan constitute a predominantly employed population representing a broad range of economic, social and educational characteristics; the population is underrepresented only by the indigent and very affluent. Women were enrolled in the study early in pregnancy when they first contacted the prenatal clinic of Kaiser Hospital in Oakland; enrollment was nearly 100 percent. About 50 percent of the women reported for prenatal care when they had been pregnant for 2 months or less. The enrollment period started in 1959 and ended in 1966. In all, 20,504 pregnant women were entered into the study population, and their pregnancies terminated in 19,044 live births and 458 stillbirths. Sixty-six percent of the women were white, 23 percent black and 11 percent of other ethnic background.

Medical data: Information on the mothers and children enrolled in the Child Health and Development Studies was derived from several sources. The mothers were extensively interviewed early in pregnancy and were interviewed again subsequently. The complete medical records of both mother and child were abstracted in detail. Information taken from the mother's record included all illnesses and conditions she had in the 15 month period including the 6 months before pregnancy and the interval corresponding to the pregnancy itself; data on all drugs prescribed in this interval were also abstracted. Information on the children was gathered from each visit the child made to any Health Plan facility or clinic (including hospitalizations) and included physician's diagnosis, prescribed treatment, laboratory test results and anthropometric measurements. The children ranged from 5 to 13 years of age when the routine abstracting of all medical records was discontinued. Additional information was derived from special examinations given by the personnel of the Child Health and Development Studies. Great efforts were exerted to follow up and ascertain the whereabouts and health of all children who did not come in for regular examinations or left the Health Plan. Information derived from outside physicians, the family, death certificates or autopsy reports was also added to the records.

Information pertaining to congenital heart disease: This information was gathered from references to heart disease in any of the child's records. Children suspected of having heart disease on this basis underwent further assessment to confirm or rule out the diagnosis. One of us (J.I.E.H.) examined all available children whose diagnosis of definite or possible congenital heart disease was based on clinical examination only; of the 104 such children examined, 32 were found to be free of heart disease. Nearly all of the children who had had cardiac surgery or catheterization were evaluated from their records although a few in this group also underwent a special Child Health and Development cardiac examination. Children who had died, and living children with a clinical diagnosis of congenital heart disease who could not be brought in for the special cardiac examination were evaluated from their medical records. In reviewing these records the examiner determined that eight children in the group did not have heart disease. Of the children classified as having congenital heart disease after these review procedures, only seven either had not been seen by a cardiologist or had not had their condition evaluated during hospitalization (at birth or subsequently).

Definitions

Congenital heart disease: We adopted the definitions used by Mitchell et al.[2] Congenital heart disease was defined as a gross structural abnormality of the heart or great vessels that is actually or potentially of functional importance. Thus, persistent left superior vena cava or aberrant right subclavian artery was not classified as congenital heart disease, nor were arrhythmias unassociated with structural malformations; complete heart block was accepted, but paroxysmal tachycardias were not. A ductus arteriosus patent in the first 14 days of life and not associated with heart failure was considered normal. The one important form of congenital heart disease not well covered by this or other studies was the bicuspid aortic valve, which is difficult to diagnose clinically; echocardiographic examination was not available while the study was in progress.

Abortion versus stillborn infant: An abortion was defined as the expulsion of the products of conception from the uterus before 20 weeks of gestation, and a stillborn infant was defined as the nonlive-born product of a pregnancy with a gestation period of 20 weeks or more. However, many stillborn infants as defined here had a fetal weight or measurements that were consistent with the diagnosis of abortion or missed abortion, even though the pregnancy did not end until some time after the 20th week. A neonatal death was defined as death of a live-born child before 28 days of age.

Definite versus possible congenital heart disease: Congenital heart disease was termed definite if the pediatric cardiologist believed there was no doubt about the diagnosis. Children considered to have definite disease included those with autopsy, surgical or cardiac catheterization verification of the diagnosis, as well as those believed to have congenital heart disease on clinical evidence alone. Those whose clinical examination or records showed neither definite congenital heart disease nor definite normality were considered to have possible congenital heart disease. The data on stillborn infants are given separately from those of live-born infants because the level of ascertainment of congenital malformations in the two groups is very different. Although there were pathology or autopsy reports on file for most of the stillborn infants, most of the pathology reports on stillborn infants of less than 28 weeks' gestation and a few for older stillborn infants were limited to descriptions of fetal size, external malformations and maceration; these give no information about internal malformations. Even when autopsy was performed, autolysis often prevented a detailed internal examination; in 55 of the autopsies there was no mention of the heart. The incidence of congenital malformations in stillborn infants is thus based on those with adequate autopsy examinations. In the remainder of this presentation, unless the findings specifically

TABLE I

Cumulative Incidence of Definite Congenital Heart Disease per 1,000 Live-Born Children Observed

Age Interval	Number of Children Undiagnosed and Under Observation at Beginning of Interval	Cumulative* Incidence of Definite Congenital Heart Disease per 1,000 Children Observed
Birth	19,044	3.3
Days		
1–6	18,838	4.0
7–31	18,256	5.2
Months		
1–2	18,011	6.4
3–5	17,516	7.3
6–11	17,108	7.8
12–23	16,472	8.3
24–35	15,455	8.7
36–47	14,620	8.9
48–59	13,850	9.1
60–71	12,926	9.1

* The rate shown for each age expresses the relative number of children with a diagnosis of congenital heart disease at that age or at younger ages.

are stated to relate to stillbirths, they pertain only to the live-born infants.

Other congenital anomalies: Congenital heart disease is often associated with other anomalies. The Child Health and Development Studies use a comprehensive definition of congenital anomalies that includes structural defects, functional abnormalities, inborn errors of metabolism and chromosomal aberrations. Because there is no agreed upon scheme for the classification of anomalies and because our intensive follow-up yields all degrees of deviation from normality, we have arbitrarily subdivided these deviations by degree, labeling them trivial, severe and nonsevere. Trivial anomalies, such as skin tags, umbilical hernias and leg-foot postural defects, are not counted as anomalies because inclusion of these minor deviations from normality would embrace a majority of all children. Severe anomalies are defined as those that are hazardous or, if not corrected, would impair the child's development or well being. The remaining anomalies, those classified as neither trivial nor severe, are labeled nonsevere. Examples of conditions coded as severe include heart disease, microcephaly, cleft lip, cystic fibrosis, mental retardation and renal agenesis. Examples of conditions classified as nonsevere are asymmetry of the face or skull, undescended testicles after age 2 years, polydactyly and ptosis palpebralis.

Results

Incidence: Definite congenital heart disease was diagnosed in 163 live-born children (Table I). The diagnoses were made or confirmed at autopsy in 39 (23.9 percent), at surgery in another 23 (14.1 percent), after cardiac catheterization in another 17 (10.4 percent) and from the clinical examination alone in 84 (51.5 percent). Another 31 children were regarded as having possible congenital heart disease; in 1 the diagnosis (of probable supravalve aortic stenosis, very mild) was made at cardiac catheterization; in the rest the diagnosis was made clinically. The life table method used in Table I adjusts for the number of children remaining under observation at each age interval. The cumulative incidence rate per 1,000 at birth and at 5 years is 3.3 and 9.1, respectively. The latter figure, 9.1, allowing for diagnosis through age 5 years, will be referred to as the adjusted rate. The comparable figure when the 31 possible cases of congenital heart disease are combined with the definite cases is 10.8.

Age at diagnosis: The number of children under observation at the beginning of each age interval, as shown in Table I, does not include children who left the Health Plan before reaching that age. Even though a great deal of follow-up information on such children is available, we cannot be sure that ascertainment of heart disease is complete for this group as a whole. All tables, therefore, pertain only to cases of congenital heart disease diagnosed while the children were under observation. However, five additional children with definite congenital heart disease were discovered through our follow-up procedures after the family had left the Health Plan. Thus, the original 19,044 live births yielded 168 patients with definite congenital heart disease, or 199 if patients with possible congenital heart disease are included. These figures in turn yield crude respective incidence rates of 8.8 and 10.4/1,000 live births, rates that differ only slightly from the adjusted rates and are comparable with the higher rates given in some other studies.[1,2] Because of the way the data on these children were obtained, it was possible to determine accurately when congenital heart disease was first suspected.

Among 163 patients with definite congenital heart disease, the disease was suspected at birth in 63 (38.7 percent) and 12 more between 1 and 6 days of age for a cumulative total of 75 infants (46.0 percent) whose disease was suspected by the end of the 1st week of life. In 22 infants the disease was suspected between age 7 and 31 days, in 23 between age 1 and 2 months, in 14 between age 3 and 5 months and in 10 between age 6 and 11 months. Thus 59.5 percent of the total were suspected of having heart disease by age 1 month, 73.6 percent by age 2 months, 82.2 percent by age 5 months and 88.3 percent by the end of the 1st year of life. Eight patients were first suspected of having heart disease in the 2nd year of life; in 6, 3 and 2

TABLE II

Number of Stillborn Infants and Incidence of Congenital Heart Disease Among Stillborn Infants Subjected to Autopsy, According to Gestational Age at Termination

Gestational Age at Termination (wk)	All Stillborn Infants (no.)	Stillborn Infants Subjected to Autopsy		
		Total no.	no. With Congenital Heart Disease	Incidence of Congenital Heart Disease per 1,000
20–27	198	20	1	50.0
≥28	253	196	16*	81.6
Unknown; birth weight >1 pound	7	5	0	0
Total	458	221†	17*	76.9

* Includes one case coded as probable congenital heart disease.
† Only 166 of the autopsy reports included descriptions of the heart.

patients, the disease was not suspected until the 3rd, 4th and 5th years of life, respectively.

Incidence in stillborn infants: The data on stillbirths are presented by gestational age and autopsy status in Table II. Among all stillborn infants subjected to autopsy the incidence of congenital heart disease was 76.9/1,000. However, if only the 166 autopsies with descriptions of the heart are considered, the incidence of congenital heart disease becomes 102.4/1,000 because all cases of congenital heart disease were in this group. The types of congenital heart lesions described for all stillborn infants are given in Table III together with comparable data from previous studies.[2,4–8]

Incidence of specific types and mortality rates: Table IV gives the incidence of the specific forms of congenital heart disease noted in this study and compares the data with those of other recent major studies.[2,8–12] There were 43 deaths of the 163 live-born children with definite congenital heart disease. Twenty-one of these deaths (12.9 percent) were in neonates,

TABLE III

Distribution of Types of Congenital Heart Disease Among Affected Stillborn Infants in Previous and Present Series

Lesion	Previous Studies (by reference numbers)						Present Series	All Series Combined	
	4	5	6	7	2	8		Frequency	%
VSD	7	17	28	11	9	15	5	92	34.7
ASD	1	1	3	3	3	13	3	27	10.2
ECD	0	0	2	7	5	4	0	18	6.8
PS	0	0	0	0	1	0	2	3	1.1
AS	0	0	0	0	0	0	0	0	0.0
Coarctation of aorta	0	0	12*	2	2	6	3†	25	9.4
TGA	0	2	17	4	0	1	0	24	9.1
Tetralogy of Fallot	1	0	1	3	1	3	0	9	3.4
Truncus arteriosus	2	0	4	4	2	4	0	16	6.0
HLH	0	0	2	0	2	2	2‡	8	3.0
HRH	0	0	0	0	2	0	1	3	1.1
SV	1	0	8§	2‖	1	5	0	17	6.4
SA	0	0	3	1	0	0	1¶	5	1.9
DORV	0	0	0	0	1	0	0	1	0.4
Miscellaneous	1	0	0	3	9	4	0	17	6.4
Total	13	20	80	40	38	57	17	265	100.0

* With ventricular septal defect.
† One with Taussig-Bing malformation; one with mitral stenosis.
‡ With double outlet right ventricle.
§ Three with cor biloculare.
‖ One with cor biloculare.
¶ With ventricular septal defect, possible endocardial cushion defect.
AS = aortic stenosis; ASD = secundum atrial septal defect; DORV = double outlet right ventricle; ECD = endocardial cushion defect; HLH = hypotrophic left heart (aortic or mitral atresia, or both); HRH = hypotrophic right heart (pulmonary or tricuspid atresia, or both); PS = pulmonary stenosis; SA = single atrium; SV = single ventricle; TGA = transposition of great arteries; VSD = ventricular septal defect.

TABLE IV

Percent Distribution of Types of Congenital Heart Disease Among Affected Live-Born Infants Reported on in Previous and Present Studies

Lesion	Previous Studies (by reference number)						Present Series	All Series Combined
	2	8	9*	10	11†	12		
VSD	32.1‡	28.1	34.6	27.1	30.1	31.0	31.3	30.3
PDA	8.3	6.5	10.6	9.5	9.8	7.1	5.5	8.6
ASD	7.4	8.3	7.3	4.3	6.4	11.2	6.1	6.7
ECD	3.6	7.4	4.5	3.0	1.4		3.7	3.2
PS	8.6	2.7	5.0§	3.8	7.7	10.8	13.5	7.4
AS	3.8	4.1	6.1	5.4	4.8	8.4	3.7	5.2
Coarctation of aorta	6.7‖	5.6	5.6	9.8	5.0	3.4	5.5	5.7
TGA	2.6	5.6	7.8	6.0	5.5	2.6	3.7	4.7
Tetralogy of Fallot	3.8	8.6	5.0	4.1	3.9	8.0	3.7	5.1
Truncus arteriosus	1.7	1.2	0.0	1.4	0.8	0.0	2.5	1.0
HLH	3.1	3.3	4.5	0.8	0.0	0.0	0.6	1.3
HRH	2.4	1.5	3.4	2.4	2.8	1.1	0.6	2.2
SV	0.7	1.5	0.0	0.0	0.0	0.0	0.6	0.3
DORV	1.0	0.0	0.0	0.0	0.0	0.0	0.6	0.2
TAPVC	0.0	2.1	2.8	0.8	1.5	0.0	0.6	1.1
Miscellaneous	13.8	13.6	2.8	21.7	20.4	16.4	17.8	17.1
Total cases	420	338	179	369	1081	464	163	3104

* Patent ductus arteriosus in premature infants excluded.
† This large series included 35 stillborn infants.
‡ Eleven with pulmonary stenosis.
§ Includes pulmonary atresia.
‖ Seven with an atrial or a ventricular septal defect.
PDA = patent ductus arteriosus; TAPVC = total anomalous pulmonary venous connection; other abbreviations as in Table III.

but only 6 of these 21 deaths were definitely due to heart disease. By contrast, 16 of the 22 deaths in older infants and children were definitely due to congenital heart disease.

Associated anomalies: Among the 163 live-born children with definite congenital heart disease 49 (30.1 percent) had associated severe anomalies and another 20 (12.3 percent) had associated nonsevere anomalies. If the 31 children with possible congenital heart disease are included, these values become 27.8 percent and 12.9 percent, respectively.

Down's syndrome: In the entire cohort of live births 37 children had Down's syndrome (definite in 36 and probable in 1), yielding an incidence of 1.94/1,000 live births. Among the 36 children with definite Down's syndrome, 9 (25.0 percent) had a diagnosis of definite and 2 a diagnosis of possible congenital heart disease. The nine definite congenital heart lesions in the children with Down's syndrome were four ventricular septal defects (one with an associated patent ductus arteriosus), two endocardial cushion defects, two complex lesions that included endocardial cushion defects, and one incompletely diagnosed lesion. There were also six definite and seven probable cases of other trisomies in the cohort with, respectively, two of six (33.3 percent) and three of seven (42.9 percent) having definite congenital heart disease.

Discussion

Incidence of congenital heart disease among stillborn infants: This study did not assess the incidence of congenital heart disease from the time of conception because abortuses less than 20 weeks of age were not evaluated. Bierman et al.[13] studied fetal wastage in Hawaii and followed up women from the 4th week of pregnancy. They noted that 22 percent of all fetal losses occurred before 20 weeks of gestation. If these abortuses have a high incidence rate of heart disease, as they do of other anomalies,[14] then the true incidence of congenital heart disease from the time of conception may be much greater than now suspected.

In our study, stillbirths accounted for 23.5/1,000 births of more than 20 weeks' gestation; this is similar to rates of 15.1 to 27.1/1,000 reported by others.[2,8,15–18] Similarly, higher rates of congenital heart disease among stillborn than among live-born infants have been described by others[2,8,9,14,18] In these studies, the observed incidence of congenital heart disease per 1,000 for stillborn and live-born infants, respectively, was 27.5 and 8.1[2], 57.2 and 5.9[8], 50 and 5.7[9] and 63.3 and 5.8[18]; and the incidence of congenital heart disease in stillborn infants in the study of Poland and Lowry[14] was 44.1/1,000 (personal communication).

Although the pattern is consistent, the incidence data among stillborn infants are rather divergent. Because ascertainment of disease in this group is highly dependent on the autopsy rate and the amount of detail given in the autopsy report itself, it is not surprising to observe such divergent rates. In our series, if all fetal deaths occurring after 20 weeks' amenorrhea were used as a denominator, we would have observed an incidence of heart disease of 37.1/1,000 fetal deaths. However, although we have on file pathology reports or autopsy data for 89 percent of these fetal deaths, the detail given in the pathology reports and in some of the autopsy data is insufficient to detect disease. Fetal weight was the main factor determining whether an autopsy was performed. Autopsy was rarely performed if the fetus weighed 500 g or less, whereas it was performed in 59 percent of cases in which the fetus weighed 501 to 1,000 g, and in 96 percent of cases in which the fetus weighed more than 1,000 g. Furthermore, the detail of the autopsy was limited in some cases because of fetal maceration. The incidence of disease observed among all stillborn infants undergoing autopsy and those with a detailed autopsy was 79.4/1,000 and 102.4/1,000, respectively. There is no reason to believe that autopsies in stillborn infants were selected in our study, consciously or unconsciously, to include those with heart disease. The true incidence of heart disease in stillborn infants is no doubt closer to the higher than to the lower rates cited.

Types of congenital lesions among stillborn infants: The types of heart disease among stillborn infants in our small series showed two major lesions—ventricular septal defect and complex lesions. The predominance of ventricular septal defect matched that in live-born children but there was a significantly greater incidence of complex disease among the stillborn than among the live-born children.

Table III shows that in other reported series there was the expected predominance of ventricular septal defect. There were also excessive numbers of infants with coarctation of the aorta, transposition of the great arteries, truncus arteriosus, single atrium and single ventricle. Aortic and pulmonary stenosis were underrepresented. The similar frequency of ventricular septal defect among stillborn and live-born children suggests that the defect was not related to the stillbirth, an hypothesis in accord with prevailing views that ventricular septal defect should cause little fetal difficulty.[19] However, the increased prevalence in stillborn infants of complex lesions such as truncus arteriosus and aortic and mitral atresia suggests either that these lesions are sometimes responsible for fetal death or that they are more likely to be associated with other factors that increase the risk of fetal death; the second possibility seems more likely.

Incidence of congenital heart disease among live born children—sources of diagnostic error: The adjusted incidence of heart disease among live-born children in this series was 9.1/1,000 for those with definite heart disease and 10.8/1,000 if those with possible heart disease are included. These figures are slightly higher than the rates of 5.7 to 8.5/1,000 live births obtained in other intensive studies.[2,8,9–12,18,20–22] Clearly, the accuracy of these data depends on the completeness of ascertainment and the correctness of the diagnoses, that is, on how many false positive and false negative diagnoses there were. In the series of Mitchell et al.,[2] only 44 percent of the diagnoses were made by clinical examination alone compared with 52 percent in our series. It is quite likely that our series includes more cases with minimal congenital heart disease that was not serious enough to justify cardiac catheterization. In our series all children were seen frequently for routine care rather than at a few set intervals; as a result, the likeli-

hood of detecting minimal lesions was enhanced. Furthermore, Mitchell et al.[2] indicate that there might have been some undetected cases of minimal disease in their group of nonrespondents.

In studies on the incidence of congenital heart disease, it is important to have a high autopsy rate on all subjects who die, especially when there has been only a short time for clinical assessment. In neonates and infants an autopsy often reveals unsuspected disease.[20] The autopsy rate among neonates who died was nearly identical in our study and that of Mitchell et al.[2] (90 percent and 89 percent, respectively).

A second major source of error could be failure to detect minimal heart disease. Thus, it is possible that many children with a small ventricular or atrial septal defect, or with mild aortic or pulmonary stenosis, could be missed. The accuracy of the clinical diagnosis of ventricular septal defect is thought to be good,[23] so that the question is mainly whether the average pediatrician recognized that the soft, "puffy" murmur[24] was not an innocent murmur but due to a tiny ventricular septal defect. Because all children in our study were examined by several pediatricians during the course of follow-up this source of error may have been minimized. Although even large atrial septal defects may be missed because the physical signs are not prominent, it is unlikely that many of these were missed in our study because any child reported to have a murmur was referred to a cardiologist and because all children in the study were seen frequently. On the other hand, small atrial septal defects with pulmonary flow less than 1.5 times systemic flow are unlikely to draw attention and are probably underestimated in any series; ignoring these defects will certainly alter the total incidence figures.

Minimal aortic or pulmonary stenosis poses more important clinical problems, and the accuracy of diagnosis of these defects affects the total incidence data from any series. In the report of Bound and Logan,[8] pulmonary stenosis was diagnosed only when there was at least a 25 mm Hg decrease in systolic pressure across the pulmonary valve, a criterion that underestimates the incidence of this lesion. In our series, semilunar valve stenoses were diagnosed definitely when there was a typical harsh ejection murmur of grade 3/6 intensity or more, an ejection click or electrocardiographic or roentgenographic changes. However, there were many children with softer murmurs that still sounded to the cardiologist as if the murmur was too rough to be attributed with certainty to an innocent murmur; some of them might have had a bicuspid aortic valve. A recent study[25] demonstrated that a congenitally bicuspid aortic valve may occur in almost 2 percent of the population. Because this is double the rate of all other heart disease, the inclusion of fewer or more cases of this lesion in any series will greatly influence the total incidence figures. Detecting these minimal lesions has other importance, namely, that of providing accurate data for etiologic correlations. The association of heart disease with viral infections or the administration of certain drugs during pregnancy might be masked if only severe examples of heart disease are detected but disclosed if all congenital heart disease is included.

Age at diagnosis of congenital heart disease: Most children in our series had their heart disease diagnosed by age 1 year, in accord with previous findings.[9,10,18] However, in only 46 percent had the diagnosis been made or suspected before age 1 week; thus data from newborn nurseries must give too low an estimate of the true frequency of heart disease.[26,27] These findings also point out the need for frequent visits to the pediatrician, especially during the 1st year of life. The early diagnosis of most forms of heart disease is advantageous to any population study of this type because disease in most children will be detected before substantial numbers move away or leave the study for other reasons.

Incidence of Down's syndrome: The incidence of chromosomal defects was less than the 4.6/1,000 live births found in a recent study.[28] However, that study included not only the defects found in grossly malformed infants but also those detected by karyotyping the remaining infants who appeared normal. The incidence of Down's syndrome in our series was similar to that noted in Liverpool[11] but greater than that observed in other large series.[28–30] However, because the incidence of this syndrome is highly dependent on the age distribution of the mothers,[31] comparisons of total rates are not really meaningful. Mitchell et al.[30] noted that for women 38 years of age or older the risk of Down's syndrome in their offspring is 1/88 births. In our study, the risk for single live-born children of women in this age group was 1/83. The risks given for this specific age group, the only one available on which comparisons could be made, are strikingly similar. Among the children in our series with a confirmed diagnosis of Down's syndrome, 25 percent had congenital heart disease, a proportion similar to that found by Mitchell et al.[30] and Kenna et al.,[11] but lower than the rate of 40 percent reported by Rowe and Uchida[32] in a more selected group of children with Down's syndrome. Lower values of 11.7 percent were reported from British Columbia.[29] The risk of having heart disease in Down's syndrome appears to be independent of maternal age[30] and thus is probably not related to whether the trisomy is due to translocation or nondisjunction. In other trisomies, the risk of disease was 33 percent, but the numbers were too small to allow any conclusions to be drawn.

Association with other congenital anomalies: Congenital heart disease is often associated with other major anomalies, and the frequency of this association depends in part on the definition and diagnosis of those other lesions. In the Liverpool study,[11] 19.8 percent of children with congenital heart disease had associated lesions compared with 30 percent in our study and in those of Mitchell et al.[2] and Feldt et al.[9] The figure from the New England Regional Infant Care Program[33] was higher (35.6 percent), but this study excluded infants without severe congenital heart disease.

Implications: In general, our figures for the incidence of heart disease as a whole and for various types of lesions agree well with data from recent intensive studies.

However, our series emphasizes the need for better evaluation of congenital heart disease in abortuses and stillborn infants and for the development of better methods of identifying minimal heart disease. More complete case findings not only would lead to more exact prevalence data but also might lead to more precise correlation with genetic and environmental factors and thus allow better understanding of the causes of congenital heart disease.

Acknowledgment

This research was initiated by the late Dr. Jacob Yerushalmy, former Director of the Child Health and Development Studies. We acknowledge his enthusiastic support and encouragement in the phases of examinations and data collection. We also thank Dr. Bea J. van den Berg, Dr. Abraham Rudolph, and Mr. Ronald Wilson for their assistance. Mr. Harald Kipp, programmer, assisted in the preparation of the tables.

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Survival of Patients With Nontransmural Myocardial Infarction: A Population-Based Study

MOYSES SZKLO, MD, Dr PH
ROBERT GOLDBERG, MS, PhD
HAROLD L. KENNEDY, MPH, MD, FACC
JAMES A. TONASCIA, PhD

Baltimore, Maryland

A population-based study was conducted in metropolitan Baltimore in which the short- and long-term prognosis of 283 patients with nontransmural myocardial infarction was compared with that of 953 patients with transmural infarction. After simultaneous adjustment for several variables, the in-hospital case fatality rate was greater for patients with transmural (30.1 percent) than with nontransmural (18.3 percent) infarction ($P < 0.01$). However, for patients discharged alive from the hospital and followed up for as long as 10 years, no significant differences in survival were found between the groups with transmural and nontransmural infarction. A multiple adjustment procedure yielded 3 year case fatality rates of 27.1 percent and 28.3 percent, respectively, for patients with transmural and nontransmural myocardial infarction surviving the acute phase.

These results suggest that the long-term prognosis of patients with nontransmural infarction is as guarded as that of patients with transmural infarction and that attempts to prevent subsequent mortality should be diligently pursued in both groups of patients.

Recent reports[1,2] have challenged the widely held view that patients who have sustained a "mild coronary" or nontransmural myocardial infarction have a better prognosis than patients who have had a transmural myocardial infarction. Previous studies[2,3] examining the prognosis of patients by type of myocardial infarction have usually examined a limited number of patients drawn from single institutions, thus raising the possibility of selection biases. Thus, there is a need for population studies of short- and long-term prognosis of patients with nontransmural myocardial infarction.

This report describes a population-based study of hospitalized patients with a myocardial infarction who were classified according to whether their infarction was transmural or nontransmural and whose survival status was ascertained for as long as 10 years after hospital discharge.

Material and Methods

Study population: This study was part of an investigation of trends over time in the prognosis of patients with myocardial infarction and included a systematic one in three sampling of patients discharged with a diagnosis of myocardial infarction (ICD codes 410.0 to 410.9, eighth revision) from hospitals in the Baltimore Standard Metropolitan Statistical Area (SMSA) during two time periods, July 1, 1966 through June 30, 1967, and January 1 through December 31, 1971. These time periods were purposely selected to permit a relatively long follow-up period after hospital discharge.

Medical records with a discharge diagnosis of myocardial infarction were obtained from 20 of the 24 Baltimore SMSA hospitals and reviewed for validation purposes. A diagnosis of transmural myocardial infarction was accepted when serum enzyme elevations and a typical clinical history were accompanied by the

This project was supported by Grant 5 P50 NS 06229 from the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland. Manuscript received February 5, 1978; revised manuscript received May 2, 1978, accepted May 17, 1978.

Address for reprints: Moyses Szklo, MD, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205.

TABLE I

Percent Distribution of Cases of Acute Myocardial Infarction by Type of Infarction and by Selected Characteristics (Metropolitan Baltimore, July 1, 1966 to June 30, 1967 and January 1, 1971 to December 31, 1971)

Characteristic	Type of Infarction: Transmural Total*	Transmural Percent With Characteristic	Nontransmural Total*	Nontransmural Percent With Characteristic	P
Age 60 years or more	952	55.5	281	63.0	<0.05
Male	950	70.4	282	63.8	<0.05
White	923	91.9	274	86.1	<0.005
Initial myocardial infarction	953	72.1	283	65.7	<0.05
Anterior myocardial infarction	866	50.9	233	73.8	<0.001
Admitted to a coronary care unit	952	73.0	283	70.0	NS
Admitted to a teaching hospital	946	20.6	280	21.8	NS
Prior history					
Angina pectoris	953	18.7	283	23.0	NS
Hypertension	953	26.1	284	33.5	<0.02
Diabetes	953	19.3	284	18.0	NS
Cigarette smoking	561	71.1	169	66.3	NS
Complications during hospitalization					
Congestive heart failure	953	25.1	283	23.0	NS
Shock	953	8.0	283	4.2	<0.05
Ventricular fibrillation or cardiac arrest	953	22.1	283	17.7	NS
Selected arrhythmias†	953	52.7	283	51.9	NS
Anticoagulant therapy during hospitalization	953	58.4	283	46.6	<0.001

* Totals vary for several variables because unknowns were excluded.
† Any of the following: atrioventricular block, left or right bundle branch block, ventricular ectopic complexes.
NS = not significant; P = probability.

appearance in serial electrocardiograms of Q waves with a duration of 0.04 second or more and an amplitude equal to or greater than 25 percent of the R wave in the same lead, as well as a typical pattern of evolutionary changes in the S-T segment and T waves. A diagnosis of nontransmural myocardial infarction was accepted when, in the absence of abnormal Q waves, ischemic S-T segment and T wave changes persisted for at least 24 hours in the presence of serum enzyme elevations and a typical clinical history. These changes consisted of either S-T segment depression of 1 mm or more (with or without symmetric T wave inversion) or symmetric T wave inversion alone.

This report is based on 1,236 patients who met the diagnostic criteria in both time periods of our study. In the 1966–67 period, 481 patients were included, of whom 95 (19.8 percent) had nontransmural myocardial infarction. In 1971, a total of 755 patients were included, of whom 188 (24.9 percent) had a nontransmural myocardial infarction.

Data collection: The hospital records of patients with a validated myocardial infarction were abstracted for clinical and demographic data, including age, complications during hospitalization and admission or nonadmission to a coronary care unit. Several approaches were used to ascertain survival status after discharge from the hospital, including review of records for additional hospitalizations, letters and telephone calls to attending physicians and to patients or their relatives, and a search of death certificates in the Baltimore Standard Metropolitan Statistical Area.

Data analysis: Short-term prognosis was examined by calculating in-hospital case fatality rates. To include patients followed up for various lengths of time after discharge from the hospital, a life table approach was chosen to examine long-term survivorship. The probability of survival from hospital discharge to each successive annual anniversary was calculated for a 10 year period, adjusting for deaths and follow-up losses.[4] The log rank test was employed to calculate the overall significance of the difference between two survival curves.[5] The simultaneous effect of several variables was accounted for by using a logistic multiple regression technique.[6]

Results

Unless otherwise specified, results are given for the 1966–67 and the 1971 periods combined. Of the 1,236 patients included in the study, 953 (77.1 percent) had a transmural and 283 (22.9 percent) had a nontransmural myocardial infarction. The two groups, respectively, had a mean age of 61.4 and 62.8 years and an average length of hospital stay of 20.6 and 19.3 days.

Baseline clinical characteristics of the two groups of patients (Table I): A significantly greater proportion of patients with transmural than of those with nontransmural infarction were male, white, those who had an initial myocardial infarction or a clinical course complicated by shock or were treated with anticoagulant therapy during the acute phase of the infarction. Patients with a nontransmural myocardial infarction included a significantly greater proportion of older subjects (60 or more years) and those with an anterior infarction and who gave a history of hypertension before the infarction. Medical care variables, such as admission to a coronary care unit or to a teaching or nonteaching hospital, did not differ significantly between the two groups.

Short-term prognosis (Table II): The ratio between the in-hospital case fatality rate in patients with transmural infarction and that in patients with nontransmural infarction was 1.7 ($P < 0.01$) when rates were simultaneously adjusted for 17 variables that may affect in-hospital mortality, including past medical history, history of prior myocardial infarction, admission to a

coronary care unit, type of hospital of admission (teaching or nonteaching) and complications during hospitalization.

Long-term prognosis: Of 925 patients discharged alive from the hospital, further follow-up could be obtained for 871 (94.2 percent). Of these, 662 (76 percent) had a transmural and 209 (24 percent) a nontransmural myocardial infarction. Among patients with further follow-up, 91 percent of those with transmural and 86 percent of those with nontransmural myocardial infarction either were followed up for at least 5 years or were known to have died within the 5 year follow-up period after hospital discharge. A 10 year follow-up was obtained for 44 percent of patients with transmural and 49 percent of those with nontransmural myocardial infarction, including those known to have died during this follow-up period.

TABLE II

Crude and Adjusted* In-Hospital Case Fatality Rates (CFR) of Patients With Myocardial Infarction by Type of Infarction (Metropolitan Baltimore, July 1, 1966 to June 30, 1967 and January 1, 1971 to December 31, 1971)

Type of Infarction	Total	Crude CFR (%)	Adjusted CFR (%)	Adjusted Risk Ratio†
Transmural	953	26.7	30.2	1.7
Nontransmural	283	19.7	18.3‡	

* Simultaneously adjusted for age (less than 60 or 60 or more years), sex, race, cigarette smoking before hospitalization, order of myocardial infarction (initial or recurrent), history of prior angina, hypertension or diabetes, location of myocardial infarction (anterior or inferior/posterior), admission to coronary care unit, type of hospital of admission (teaching or nonteaching), use of anticoagulant agents during the acute phase of infarction, occurrence during the acute phase of congestive heart failure, shock, ventricular fibrillation or cardiac arrest, ventricular tachycardia and other selected arrhythmias (any of the following: atrioventricular block, left or right bundle branch block and ventricular ectopic complexes) and study period (1966 to 1967 or 1971).

† Ratio between in-hospital case fatality rate of patients with transmural myocardial infarction and that of patients with nontransmural myocardial infarction.

‡ P (probability) <0.01.

Survival rates for hospital survivors observed during both time periods are shown in Figure 1. Patients with nontransmural myocardial infarction had a slightly poorer long-term survivorship than those with transmural infarction (the overall difference was of borderline statistical significance [P <0.10]). A similar survival trend was observed when the same analysis was carried out separately for the 1966–67 and the 1971 periods.

Since patients in the groups with transmural and nontransmural infarction differed in regard to several variables (Table I), a multiple adjustment was carried out for the mortality occurring in the first 3 years of follow-up after hospital discharge. This analysis included only patients with a complete 3 year follow-up, comprising 95 percent of the 871 hospital survivors with further follow-up. These 3 year mortality rates, simultaneously adjusted for time period and for demographic, clinical and medical care variables (Table III), confirm the pattern illustrated in the long-term survival curve (Fig. 1) of no significant differences between survivor-

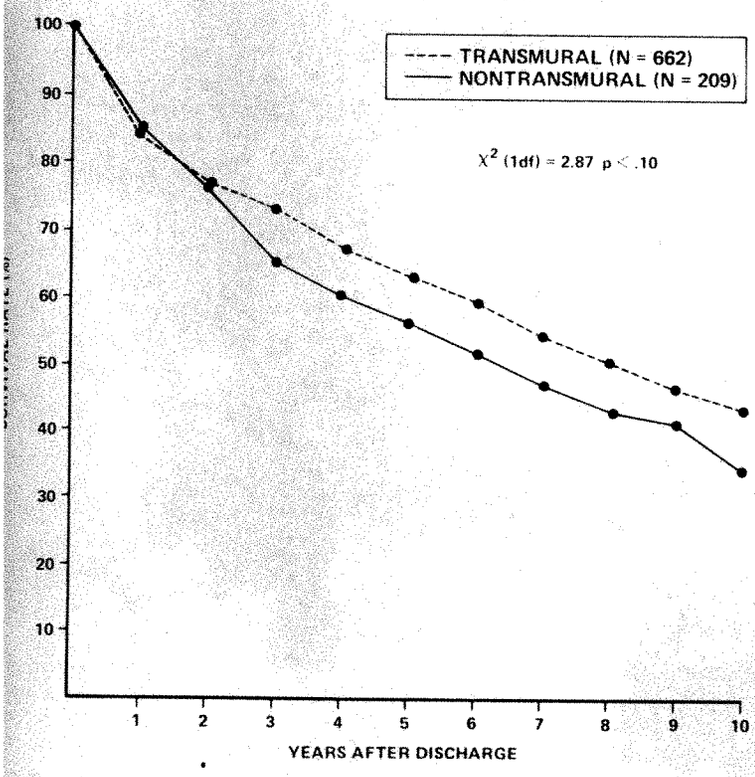


FIGURE 1. Survival rates in patients discharged alive after transmural and nontransmural acute myocardial infarction in metropolitan Baltimore during two time periods (July 1, 1966 to June 30, 1967 and January 1, 1971 to December 31, 1971).

ship of patients with transmural and nontransmural myocardial infarction.

Discussion

The results of this population-based study suggest that although the in-hospital course of patients with transmural myocardial infarction in the time periods examined was poorer than that of patients with nontransmural myocardial infarction, the long-term prognosis of hospital survivors was similar for patients with both types of myocardial infarction. These results were independent of several factors that may affect survival after an acute myocardial infarction, including clinical complications during the acute phase and admission to a coronary care unit or a teaching or nonteaching hospital.

Studies of the outcome of patients with transmural or nontransmural myocardial infarction have usually been based on relatively small clinical series obtained from single institutions,[1,2] thus raising the possibility that selection biases may have occurred. By including a sample of most hospitalized cases of myocardial infarction in metropolitan Baltimore, our study decreased the likelihood of such biases. Also, unlike many studies, our study allowed ascertainment of survival status of patients for as long as 10 years, and employed a life table approach to analyze survival, thereby adjusting for different lengths of follow-up.

Prognosis: The finding that the in-hospital case fatality rate was greater for patients with a transmural than for those with a nontransmural myocardial infarction is consistent with the widely held view reported in many studies.[1,2,7] Acute nontransmural myocardial infarction has traditionally been regarded as a relatively benign event associated with a milder uncomplicated course and an expected good long-term prognosis.[8,9] However, our study as well as other recent studies have challenged this view. Rigo et al.,[2] for example, followed up 159 patients discharged from the Johns Hopkins Hospital coronary care unit, and showed that there was no difference between the survival of patients with transmural and nontransmural myocardial infarction after an average follow-up period of 20.2 months. Moreover, Cannom et al.,[1] in their study of 188 patients admitted to Yale-New Haven Hospital, demonstrated that although there was a slightly greater in-hospital mortality among patients with transmural versus nontransmural infarction, the 40 month survival rate among hospital survivors was significantly lower for patients with nontransmural than for those with transmural infarction (53 and 70 percent, respectively). Other authors[7,10] have reported similar findings.

Reasons for difference between short-term and long-term prognosis: It is not clear why the long- but not the short-term prognosis of patients with nontransmural myocardial infarction is similar to, or even worse than, that of patients with transmural myocardial infarction. A greater in-hospital case fatality rate among patients with transmural myocardial infarction is consistent with the fact that prognosis in the acute phase of infarction seems to be mainly determined by the extent of the total acute myocardial damage and its hemodynamic and pathophysiologic consequences.[11,12] However, it is possible that once the acutely infarcted area heals, the anatomic coronary artery disease, known to be a determining factor in the long-term prognosis of such patients, progresses at the same pace in both groups of patients. A recent study by Madigan et al.[13] supporting this hypothesis showed that as many as 60 percent of patients with nontransmural myocardial infarction had double or triple vessel disease and all had significant (greater than 75 percent) narrowing of at least one major coronary vessel.

Another hypothesis to explain the relatively poor long-term prognosis of patients discharged after an acute episode of nontransmural myocardial infarction was recently advanced by Vaisrub[14] who suggested that collateral circulation, which seems to be more frequent in survivors of nontransmural than of transmural infarction,[15] would prevent necrosis but keep alive an ischemic periinfarction zone, thus favoring the development of angina and potentially lethal ectopic complexes. This hypothesis is supported by findings that the incidence rates of angina pectoris, recurrent infarction and sudden death are higher among patients discharged alive after an acute nontransmural myocardial infarction than among those with transmural myocardial infarction.[16] A similar view is shared by Cannom et al.,[1] who suggested that patients with nontransmural myocardial infarction without a transmural scar may well be more prone to recurrent ischemic events with electrophysiologic subendocardial ischemia resulting in lethal arrhythmias.

Implications: Our study confirms in a total urban population the suggestion from studies carried out in single institutions that the long-term prognosis of patients with nontransmural myocardial infarction may be as guarded as that of patients with transmural myocardial infarction. This finding is somewhat analogous to that of patients with coronary insufficiency or those admitted with chest pain without infarction[2] in that they have a good short-term outcome but seem to

TABLE III

Crude and Adjusted* 3-Year Case Fatality Rates (CFR) of Patients With Myocardial Infarction Discharged Alive From the Hospital by Type of Infarction (Metropolitan Baltimore, July 1, 1966 to June 30, 1967 and January 1, 1971 to December 31, 1971)

Type of Infarction	Total	Crude CFR (%)	Adjusted CRF (%)	Adjusted Risk Ratio†
Transmural	627	25.2	27.1	
			NS	0.96
Nontransmural	199	34.0	28.3	

* Simultaneously adjusted for the variables listed in Table II.
† Ratio between 3 year case fatality rate of patients with transmural myocardial infarction and that of patients with nontransmural myocardial infarction.
NS = difference not significant.

fare as poorly in the long run as patients with definite myocardial infarction.[17,18] This suggests that new interest is warranted in the pathogenetic mechanisms of "incomplete" infarction syndromes. The finding that the "mild" infarction may have a poorer prognosis than previously suspected has important practical implications. Efforts aimed at prevention of lethal arrhythmias and death should be as diligently pursued in cases of nontransmural as in those of transmural infarction.

Acknowledgment

We are indebted to Balinda Scott, Gregory Kruse, Alan Martinson, Mary Pitt and Ilene Roberts for help in data collection and analysis, to Susan Tonascia for valuable editorial suggestions and to Sidney Norton for help with the death certificate search. This study was made possible by the interest and cooperation of the medical record rooms, administrations and cardiology departments of Baltimore hospitals, and physicians in the Baltimore area.

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Relation of Lipids, Weight and Physical Activity to Incidence of Coronary Heart Disease: The Puerto Rico Heart Study

RAUL COSTAS, Jr., MD*
MARIO R. GARCIA-PALMIERI, MD, FACC*
EMILIO NAZARIO, MS*
PAUL D. SORLIE, MS†

San Juan, Puerto Rico
Bethesda, Maryland

The 2 1/2 year incidence of coronary heart disease was examined in relation to antecedent serum cholesterol and fasting triglyceride levels, physical activity status and relative weight in a cohort of 8,171 urban and rural men 45 to 64 years old participating in the Puerto Rico Heart Program. In this population with a low incidence rate of coronary heart disease, risk of coronary disease was related to serum cholesterol in both urban and rural groups, but this trend was statistically significant only in the urban population. Neither the urban nor the rural population showed a substantial or statistically significant association of serum triglyceride levels with incidence of coronary heart disease.

Correlations among relative weight and serum triglyceride and serum cholesterol levels were noted. Despite small differences in incidence of coronary heart disease between urban and rural groups, values for serum cholesterol, triglycerides and relative weight were all significantly higher in the urban men. Only physical activity levels were higher in the rural men. Multivariate analysis, performed to sort out the net effects of these interrelated variables, revealed that serum cholesterol is related to the risk of coronary heart disease even when all variables are taken into account. Low levels of physical activity were significantly associated with a greater incidence of coronary heart disease only in urban men ($P < 0.05$). Overweight, which was associated with higher lipid values and less physical activity, was not related to the development of coronary heart disease in either the urban or the rural cohort.

The population of Puerto Rico has several features that permit a unique investigation into the etiology of coronary heart disease. The average Puerto Rican leads a much less sedentary life than his counterpart in the mainland United States; he is also much leaner.[1,2] Laboratory determinations have indicated that serum cholesterol levels are lower in Puerto Rican men and that fasting triglyceride levels may be higher (Table I). Thus, there is a group of interrelated variables (lipids, relative weight and physical activity) that manifest themselves quite differently in Puerto Rico than in the United States. These variables have been shown to be related to incidence of coronary heart disease in areas where this incidence rate is high.[3–9] However, their influence on the risk of coronary heart disease in areas with a low incidence rate and lower risk factor levels is not as well established.[1,10]

Within Puerto Rico itself there are groups that show sizable and statistically significant differences in risk factors for coronary heart disease. Persons living in the urban areas around the city of San Juan have higher levels of fat ingestion and higher values for relative weight, serum cholesterol and serum triglycerides than those living in the hilly and predominantly agricultural interior of the island.[11] In contrast, calorie

From the Department of Medicine, School of Medicine, University of Puerto Rico, San Juan, Puerto Rico* and the Biometrics Research Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.†
This study was supported by contract PH-43-63-620 of the National Heart, Lung, and Blood Institute of the U. S. Public Health Service, National Institutes of Health, Bethesda, Maryland. Manuscript received August 19, 1977; revised manuscript received May 23, 1978, accepted May 24, 1978.
Address for reprints: Raul Costas, Jr., MD, Programa de Salud del Corazón, Apartado "10697," Caparra Heights Station, San Juan, Puerto Rico 00922.

TABLE I

Mean Relative Weight, Serum Cholesterol, Serum Triglyceride and Incidence of Coronary Heart Disease (CHD) in Framingham and Puerto Rico (Men aged 50 to 59 Years)

	Puerto Rico	Framingham
Relative weight (%)	113	120
Serum cholesterol (mg/dl)	191	219
Serum triglyceride (mg/dl)	164	154
CHD incidence (rate/1000 per yr)	3.5	9.5

Source: Serum cholesterol and serum triglyceride comparisons are from the Cooperative Lipoprotein Phenotyping Study,[2] relative weight and incidence of coronary heart disease are from "Differences in coronary heart disease in Framingham, Honolulu and Puerto Rico."[1]

TABLE II

Mean Values of Selected Characteristics at Initial Examination: Puerto Rico Heart Health Program (mean ± standard deviation)

	Rural*		Urban*	
	45–54 Years	55–64 Years	45–54 Years	55–64 Years
Fasting triglycerides (mg/dl)	127 ± 68	130 ± 83	171 ± 150	148 ± 104
Serum cholesterol (mg/dl)	195 ± 37	196 ± 40	207 ± 42	203 ± 42
Relative weight (% of ideal)	105 ± 16	103 ± 16	117 ± 18	114 ± 19
Physical activity index†	39 ± 11	37 ± 10	31 ± 7	31 ± 7

* All urban-rural differences are statistically significant from zero at the 0.01 level.
† 24 = no activity.

consumption per unit of body weight and physical activity are greater in the rural areas.

Correlations among lipids, relative weight and physical activity have been documented in earlier reports.[12] In both urban and rural men, serum cholesterol was positively correlated with triglyceride levels and relative weight. Triglyceride levels were also associated with relative weight and had a negative correlation with physical activity. Relative weight was the most significant variable in explaining urban-rural differences in serum lipids.[13]

Thus, in Puerto Rico, the lipids, relative weight and physical activity levels are distributed with a frequency different from that found on the United States mainland; these variables are correlated; and in some studies elsewhere, they have been found to be associated with incidence of coronary heart disease. This report concerns the relation of these variables to the development of coronary heart disease in men in the Puerto Rico Heart Study.

Materials and Methods

Initial examination: The Puerto Rico Heart Study, in operation since 1965, has followed up urban and rural men aged 45 to 64 years who were examined and found free of coronary heart disease at the initial examination. At the time of the initial examination, each subject had routine determinations of serum cholesterol (Huang et al.[14]), weight and physical activity index. Relative weight, expressed as a percent, was computed as the ratio of the observed weight to the ideal weight (from Metropolitan Life Insurance tables[15]). The physical activity index was based on the weighted number of hours spent in each of five physical activity levels.[16] Triglyceride levels were determined by the method of Van Handel and Zilversmit.[17] There were 2,395 rural and 5,776 urban men free of coronary heart disease at the initial examination who had known values for serum cholesterol, weight and physical activity. For analyses that include triglyceride, only values for men who came to the examination fasting are included (1,497 rural and 3,473 urban men).

Follow-up: The subjects were reexamined in a clinic established especially for the study. Between examinations, 146 new coronary events had occurred. New coronary events were defined as electrocardiographic or serum enzyme evidence of myocardial infarction, certified coronary deaths reviewed by study personnel and cases of angina pectoris diagnosed from a standardized history. Specific criteria have been provided elsewhere.[18]

Incidence rates of coronary heart disease were determined in groups of subjects categorized by levels of risk attributes, age and residence in urban or rural areas. Age adjustment of incidence rates was done by direct adjustment using equal weights applied to the rates in age-specific groups spanning 10 years. Regression analysis using the logistic model was carried out to assess the association of the variables with incidence of coronary heart disease.

Results

Serum triglycerides: The mean levels of fasting triglycerides are given in Table II, which shows significantly higher values for the younger urban group ($P < 0.01$). Standardized determinations from the Cooperative Lipoprotein Phenotyping Study indicate that serum triglyceride levels are higher in Puerto Rico than in the Framingham and Albany study populations in the United States.[2] However, this unique distribution of triglycerides did not reveal any clear associations with incidence of coronary heart disease. Figure 1 shows the association between coronary heart disease and triglyceride levels in terms of incidence rates of coronary disease for categories of triglyceride levels and in terms of an average regression coefficient (β) from the logistic model. Regression coefficients were computed for the age groups 45 to 54 years and 55 to 64 years and then were weighted by the inverse of their variance to form an average coefficient. If the t value (the ratio of the coefficient to its standard error) is greater than 1.96, then the coefficient is considered statistically significant from 0 at the 0.05 level. Although the relations seen in this figure are not statistically significant, low levels of triglycerides (under 100 mg/dl) do show the lowest incidence. However, if allowance is made for the association of triglycerides with serum cholesterol, the average coefficient in the urban area becomes very small in magnitude and negative in direction.

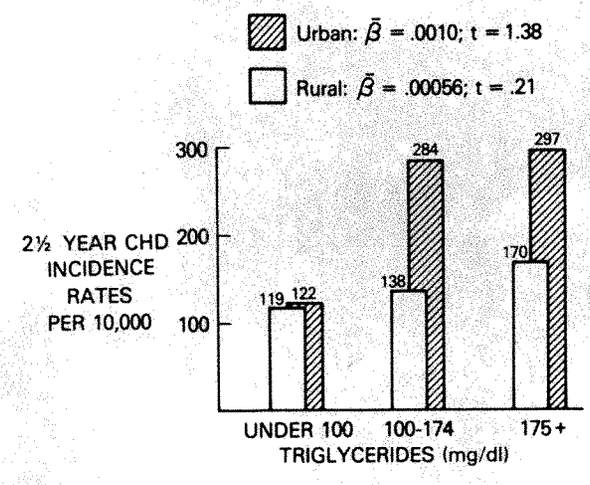


FIGURE 1. Age-adjusted 2 1/2 year incidence of coronary heart disease by fasting triglyceride level at examination 1; men aged 45 to 64 years. β = average regression coefficient for triglyceride level in the logistic model; CHD = coronary heart disease; t = average regression coefficient divided by its standard error.

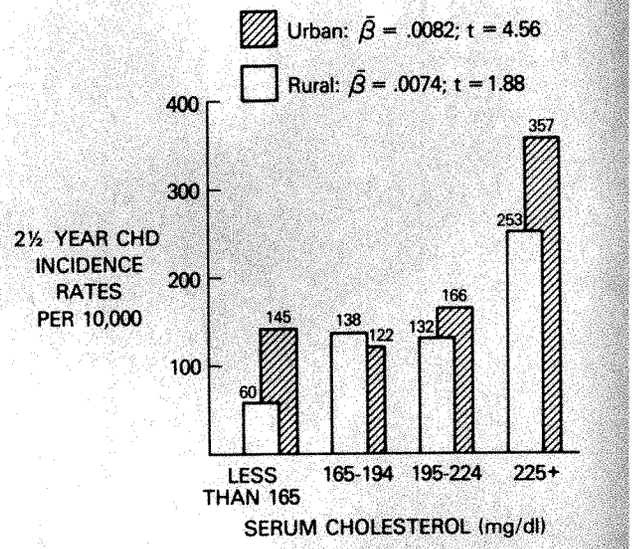


FIGURE 2. Age-adjusted 2 1/2 year incidence of coronary heart disease by serum cholesterol level at examination 1; men aged 45 to 64 years. β = average regression coefficient for serum cholesterol in the logistic model; other abbreviations as in Figure 1.

TABLE III

Age-Adjusted Incidence of Coronary Heart Disease per 10,000 by Level of Serum Cholesterol (Rural and Urban)

Serum Cholesterol Level	Rural		Urban	
	Population At Risk	Age-Adjusted Incidence Rate	Population At Risk	Age-Adjusted Incidence Rate
−164	504	59	888	144
165–179	343	171	699	87
180–194	394	100	901	155
195–209	383	102	894	90
210–224	305	162	752	229
225–239	198	146	610	285
240–254	139	356	439	301
255–269	65	305	240	476
270+	72	273	379	398

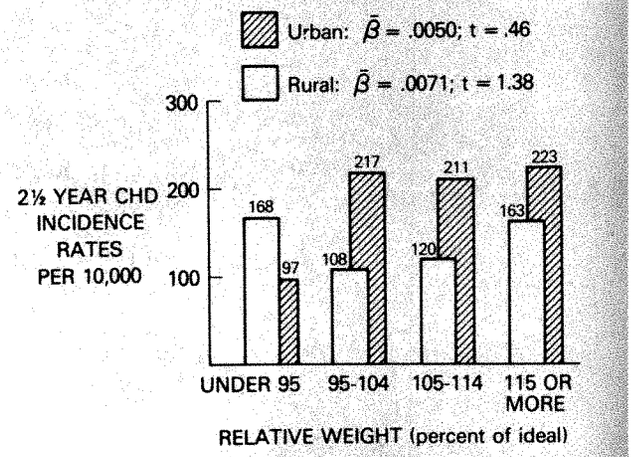


FIGURE 3. Age-adjusted 2 1/2 year incidence of coronary heart disease by relative weight at examination 1. $\bar{\beta}$= average regression coefficient for relative weight in the logistic model. Other abbreviations as in Figure 1.

Serum cholesterol: In contrast to serum triglycerides, serum cholesterol levels are lower in Puerto Rico than in the United States.[2] Over this lower distribution of cholesterol, there is a statistically significant relation between cholesterol level and incidence of coronary heart disease (Fig. 2). The strength of the association, as measured from the size of the regression coefficients, is similar in both the rural and urban groups. The risk of coronary heart disease increases with increasing cholesterol levels, with at least a twofold increase from the lowest to highest categories. From the follow-up data reported here, it is not clear whether there is a gradient of risk by level within the lower categories of serum cholesterol (Table III).

Relative weight: Relative weight levels (measured as percent of observed weight to ideal weight) are lower in Puerto Rico than in the Framingham population,[1] and within Puerto Rico levels of relative weight are lower in rural than in urban men ($P < 0.01$, Table II). In this population there is no association between relative weight and incidence of coronary heart disease (Fig. 3). Among men with very low levels of relative weight, the evidence is contradictory: In those from rural areas, the incidence rate of coronary disease is high, whereas it is lowest in those from urban areas. Analysis of the data for the more obese group revealed no excess risk of coronary heart disease at relative weight levels as high as 145 or more in the urban area. The rural area had too few men at these high levels for meaningful analysis.

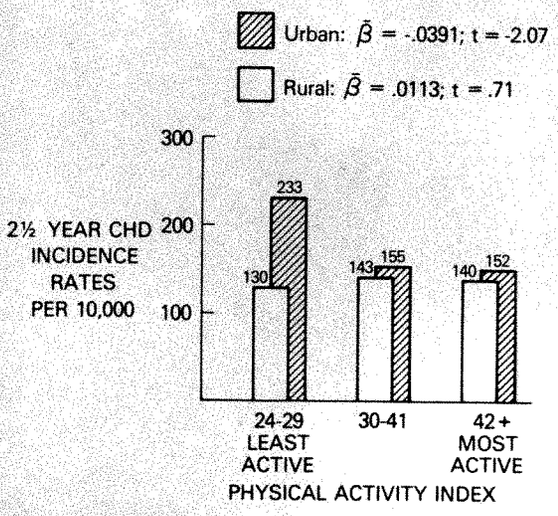


FIGURE 4. Age-adjusted 2 1/2 year incidence of coronary heart disease by physical activity index at examination 1. β= average regression coefficient for physical activity index in the logistic model. Other abbreviations as in Figure 1.

TABLE IV

Correlation Among Serum Cholesterol, Triglycerides, Physical Activity and Relative Weight: Fasting Subjects, Puerto Rico Heart Health Program

	Simple Correlation Coefficients		
	Triglycerides	Physical Activity	Relative Weight
Rural			
Age 45–54 years			
Serum cholesterol	0.41*	−0.01	0.26*
Triglycerides		−0.08*	0.39*
Physical activity			−0.16*
Age 55–64 years			
Serum cholesterol	0.50*	−0.10*	0.19*
Triglycerides		−0.17*	0.36*
Physical activity			−0.02
Urban			
Age 45–54 years			
Serum cholesterol	0.43*	0.00	0.10*
Triglycerides		−0.08*	0.19*
Physical activity			−0.09*
Age 55–64 years			
Serum cholesterol	0.36*	−0.03	0.15*
Triglycerides		−0.06*	0.21*
Physical activity			−0.09*

* Correlation significant at the 0.01 level.
Each number shows the linear relation (simple correlation coefficient) between the variable naming its row and the variable naming its column.

Physical activity: Low levels of physical activity, as measured by a physical activity index, were associated with increased risk of coronary heart disease only in urban dwellers and in the most sedentary men. The trend is statistically significant (Fig. 4).

Correlation of four risk factors: The interrelation among these four variables has been explored in detail in a previous report.[12] The correlation matrixes for these variables (Table IV) show sizable correlations between serum cholesterol and triglyceride levels as well as between lipids and relative weight. The correlation of triglyceride levels with relative weight is greater than for cholesterol level with relative weight at all ages.

Serum cholesterol in both rural and urban areas and physical activity in the urban area were related to incidence of coronary heart disease when analyzed univariately (Fig. 1 and 4). However, because the variables under consideration are correlated, multivariate analysis was required to determine if these variables were associated with incidence of coronary heart disease when all were taken into account. Table V presents the multivariate logistic coefficients for incidence of coronary heart disease in relation to serum cholesterol, physical activity and relative weight. The coefficients are standardized (coefficient times standard deviation of variable) to put them on the same scale so that the size of the coefficients can be directly compared. The coefficients for cholesterol are clearly the largest. When all of the variables are taken into account, the association between cholesterol and coronary heart disease remains statistically significant, but that between physical activity and coronary disease does not. The independent effect of cholesterol was significant in the urban population at all ages, and in the younger rural group.

TABLE V

Risk of Coronary Heart Disease According to Serum Cholesterol Level, Relative Weight and Physical Activity, 2 1/2 Year Follow-up (standardized coefficients of the multivariate logistic function)

	Rural		Urban	
	45–54 Years	55–64 Years	45–54 Years	55–64 Years
Serum cholesterol	0.548*	0.144	0.273*	0.402*
Physical activity	0.166	0.107	−0.213	−0.259
Relative weight	−0.081	0.073	−0.084	0.231
Cases/population at risk	12/1225	21/1170	58/3417	55/2359

* $P < 0.05$.

Discussion

Serum cholesterol versus triglycerides: In common with studies in populations with a large incidence of coronary heart disease, the study in Puerto Rico revealed that the incidence of the disease was related to serum cholesterol level even in the rural sample in which the incidence rate of disease is lowest (Fig. 2). Triglyceride values, unlike cholesterol, were not significantly related to this incidence in either urban or rural population samples. Furthermore, when all variables were taken into account, cholesterol continued to have an important independent contribution whereas triglycerides did not. In Figure 1, the urban area shows a seemingly high excess of coronary heart disease with triglyceride values greater than 100 mg/dl; however,

there is no *smooth* gradient of risk with increasing triglyceride values and the deficit of disease among men with triglyceride values under 100 mg/dl could be due to chance variation. The rural area shows a very slight increase in incidence of coronary heart disease by triglyceride level but, as stated before, the trend is small and not statistically significant from 0. These findings suggest that, at least in an area with a low incidence rate of coronary heart disease, triglyceride levels do not appear to be as important a contributor to the disease as other reports claim.[8,20]

The lack of association of triglyceride levels with coronary heart disease is substantiated by observations in other studies. Among subjects with inborn errors of lipid metabolism, atherosclerosis appears earlier and more frequently in those with elevated serum cholesterol levels than in those with isolated hypertriglyceridemia.[21] In animals, atherosclerotic lesions can be produced by feeding cholesterol but not by raising triglyceride levels alone.[22,23] In international comparisons, a fairly good correspondence between the cholesterol distribution and mortality from coronary disease has been demonstrated.[10] The correlation between triglyceride levels and coronary mortality, on the other hand, is most erratic.[8] Puerto Rico, for example, is an area with a documented low incidence rate of coronary heart disease by comparison with Framingham,[1] yet the triglyceride values are considerably higher (Table I).

Role of physical activity: Although it was not possible to demonstrate that the level of physical activity in this population was related to incidence of coronary heart disease, several deficiencies in the analysis must be considered. Other studies that have shown a relation between physical activity and coronary disease have demonstrated this largely for coronary fatalities with very little relation to angina pectoris.[24] The sparseness of data precludes such a detailed analysis in the Puerto Rico cohort. There was apparently some excess morbidity in the very sedentary urban population, which may achieve significance on further follow-up. It also must be pointed out that the assessment of physical activity was rather crude, and the data cannot be related to physical fitness.

Role of obesity: Although this study has demonstrated no relation between obesity and the development of coronary heart disease, other studies have.[25,26] However, when such relations have been found, there has been only a small unique contribution of obesity as such.[25] Many studies of hospitalized patients have shown no relation of obesity to myocardial infarction.[27] The data available at this length of follow-up do not allow analysis in this detail, and relations to angina and sudden death may well exist.

Implications: Of the factors under consideration, only serum cholesterol is a ubiquitous independent contributor to risk of coronary heart disease, at all ages, in areas of low as well as high incidence rates of coronary heart disease and in urban and rural populations. This finding is consistent with the commonly held view that blood cholesterol is a basic contributor to atherosclerosis.

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Role of Exercise Stress Testing in Healthy Subjects and Patients With Coronary Heart Disease

Controversies in Cardiology—I

STEPHEN N. MORRIS, MD, FACC
PAUL L. McHENRY, MD, FACC

Indianapolis, Indiana

The value of the exercise stress test in the evaluation of clinically healthy subjects and patients with coronary heart disease is not limited to the isolated interpretation of abnormalities of the S-T segment. Other measurable parameters which are of diagnostic and prognostic importance include: (1) a decrease in systolic blood pressure during exercise; (2) the appearance of complex ventricular arrhythmias at low exercise heart rates; (3) the appearance of inverted U waves during or after exercise; (4) the patient's maximal exercise capacity; and (5) new auscultatory findings postexercise. The reliability of the exercise test as a diagnostic tool is further enhanced by proper patient selection and careful attention to exercise techniques. Subjects with labile ST-T wave changes during standing hyperventilation, fixed ST-T changes at rest, and intraventricular conduction defects are not ideal candidates for "diagnostic" stress testing and the examining physician must rely more heavily on nonelectrocardiographic findings. The criteria used to define an abnormal S-T response will vary according to the lead system used. However, in both symptomatic and asymptomatic subjects the appearance of marked degrees of S-T depression at low exercise heart rates significantly increases the probability of finding advanced coronary disease, particularly if the S-T depression is seen in multiple monitoring leads and is of prolonged duration postexercise.

The value of the exercise stress test in the diagnosis of coronary artery disease is still questioned by some physicians[1]; nevertheless, those who have the most clinical and investigative experience with exercise stress testing remain convinced that the test is a great aid in the diagnosis and pathophysiologic assessment of patients with coronary artery disease.[2–5] Many of the physicians who find the exercise stress test of little value in such patients view the exercise electrocardiogram and the exercise stress test as synonymous and tend to use the exercise test for the sole purpose of confirming or excluding S-T segment abnormalities.[6,7] The exercise electrocardiogram represents only one part of the overall exercise stress test. If a diagnosis of coronary artery disease has not previously been confirmed, then the physician should strive to obtain additional diagnostic information from the exercise test. However, many diagnostic variables other than the S-T segment change must be observed and recorded.[3–5,8] These variables then become invaluable to the physician in outlining a rational approach toward patient management.[8] In failing to appreciate the value of other diagnostic findings, physicians often allow the exercise stress test to be carried out at a technician level.

Many of the misconceptions about the value of the exercise test have arisen from investigative reports on populations that are outside the 90th percentile of the population at large.[6,9] The highly selected populations referred to large medical institutions rarely reflect the populations seen

From the Krannert Institute of Cardiology, the Department of Medicine, Indiana University School of Medicine and the Veterans Administration Hospital, Indianapolis, Indiana. This study was supported in part by the Herman C. Krannert Fund; by Grants HL-06308 and HL-07182 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland; and by the American Heart Association, Indiana Affiliate, Inc. Presented at the 27th Annual Scientific Session, the American College of Cardiology, Anaheim, California, March 1978, Controversies in Cardiology. Manuscript received June 6, 1978, accepted June 19, 1978.

Address for reprints: Stephen N. Morris, MD, Department of Medicine, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46202.

TABLE I

Coronary Cineangiographic Results in 75 Presumably Healthy Men with Abnormal S-T Segment Responses to Exercise[10]

Coronary Arteries	Patients (no.)
Normal	27 (36%)
Abnormal*	48 (64%)
One vessel disease	14
Two vessel disease	17
Three vessel disease	17

* Fifty percent or greater arterial obstruction.

at the primary care level where the majority of diagnoses of coronary heart disease are made. In many of the exercise studies reported from these institutions, the patients who would optimally benefit from a diagnostic exercise test have already been screened out and the data generated become irrelevant to the practicing physician.

The physician who utilizes the exercise stress test for the diagnosis of coronary heart disease must be aware that the test has limitations, and these limitations will vary in different patient subgroups. The reliability of the exercise test as a diagnostic tool is greatly enhanced when it is utilized selectively and the data are interpreted appropriately, a simple logic that holds true for virtually all testing procedures used in clinical medicine. The purpose of this report is to outline the current strengths and weaknesses of the exercise test so that practicing physicians can utilize the test more intelligently and thus obtain optimal results.

Role of Exercise Test in Evaluating Presumably Healthy Subjects

The use of exercise testing in the clinically normal population has been criticized by some physicians because a sizable proportion of the abnormal S-T segment responses observed occur in the absence of significant coronary artery disease.[6,7] They are convinced that this problem overrides the proved value of the exercise test for isolating the subgroup of presumably healthy subjects who are at the greatest risk of having symptomatic coronary artery disease. The true incidence of false positive S-T segment responses in the presumably healthy population is yet to be defined. Previous reviews of this subject have relied almost exclusively on the reports by Borer[6] and Froelicher[9] and their co-workers. These studies dealt with highly selected populations that are not representative of the population at large. In both studies the incidence rate of cineangiographically significant coronary artery disease in subjects with a positive S-T segment response to exercise was approximately 40 percent. The study reported by Erikssen et al.[10] in 1976 provides perhaps the best available data on this subject. They studied some 2,000 men between the ages of 40 and 59 years from five different companies and government agencies in Oslo, Norway. Patients with known heart disease, hypertension under treatment with drugs, diabetes mellitus and other significant noncardiac diseases were initially excluded. Of the remaining eligible men who were asked to participate in the survey, 86 percent reported for examination. The authors identified 75 subjects who had no signs or symptoms of heart disease but who demonstrated an abnormal S-T segment response during or after exercise. Coronary cineangiographic studies demonstrated significant coronary artery disease (stenosis of 50 percent or greater) in 48 of these subjects (64 percent). Of even greater significance, the majority had double or triple vessel coronary disease (Table I).

TABLE II

Variables Observed During Exercise Testing That Have Been Correlated With Multiple Vessel Coronary Artery Disease and an Increased Risk of Subsequent Myocardial Infarction or Cardiac Death

A. Onset of abnormal S-T depression* at low exercise heart rate (heart rate less than 130/min or 70 percent of predicted maximal)
B. Pronounced S-T depression at low exercise heart rate or work load
   1. More than 2 mm S-T depression*
   2. Downsloping S-T depression
   3. Postexercise S-T depression* persisting more than 5 minutes
C. Abnormal systolic blood pressure response with progressive exercise
   1. Flat response (less than 10 mm Hg rise for two stages)
   2. Sustained decrease of more than 10 mm Hg
D. Frequent or complex ventricular arrhythmias at a low exercise heart rate or work load
E. Reduced maximal exercise heart rate or work load
   1. Inability to complete Bruce stage II or equivalent
   2. Maximal heart rate 70 percent or less of predicted maximal

* Refers to 1 mm or greater horizontal or downsloping S-T segment depression.

There are several potential reasons why the results of this study differed so significantly from those of Borer et al.[6] and Froelicher et al.[9] Erikssen et al.[10] attempted to identify those subjects with labile ST-T wave changes before exercise and excluded these subjects from the study. There is considerable evidence that this phenomenon may be the cause of a number of the false positive S-T segment responses observed with exercise testing.[11] A search for subjects with labile S-T or T wave changes during *standing* hyperventilation is important in identifying persons who may be prone to false positive S-T responses during exercise. The mean age of the subjects in the study of Erikssen et al. was greater than in the studies of Borer and Froelicher, and the former workers found a greater incidence of true positive S-T segment responses in patients over the age of 45 years. Erikssen et al. also used a different exercise protocol and a different lead system, and these factors may have contributed to the disparity of results.

Those physicians opposed to the use of exercise testing for screening the presumably healthy population are still disturbed by a 36 percent incidence rate of false positive S-T segment responses.[1,7] They argue that a false positive exercise test may lead to unwarranted psychologic trauma to the subject who does not have coronary artery disease.[7] They fail to recognize that any such psychologic trauma is usually physician-induced and not test-induced. The subject's psychologic reaction to a test result will depend on how the physician pre-

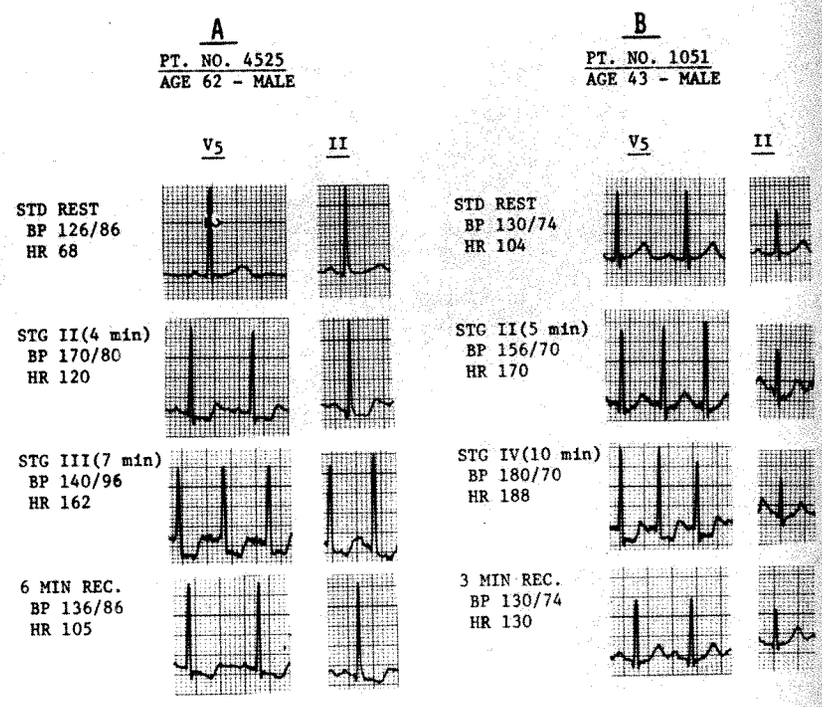


FIGURE 1. Exercise stress tests of two presumably healthy men aged 62 **(A)** and 43 **(B)** years, respectively. **A,** slightly downsloping S-T depression is present in bipolar leads II and V_5 at a low work load and exercise heart rate (stage [STG] II). Pronounced S-T depression is present at peak exercise (stage III) and prolonged S-T depression after exercise. A progressive decrease in systolic blood pressure was recorded during exercise and occasional multifocal premature ventricular complexes were noted after exercise. Coronary cineangiographic studies revealed a 75 percent stenosis in the left main coronary artery. **B,** more than 2 mm of slightly downsloping S-T depression is noted in lead V_5 but only at maximal exercise (stage IV). No other abnormalities were observed during or after the exercise test. Coronary cineangiographic studies revealed a 75 percent stenosis in the left circumflex artery. BP = blood pressure; HR = heart rate; PT. = patient; REC. = recovery; STD = standing.

sents the results to him. In the asymptomatic subject an abnormal exercise test is really a measure of his potential risk for the future development of coronary heart disease and the results should be presented in this context.

Other exercise responses to differentiate true positive from false positive exercise tests: Some physicians mistakenly look on all abnormal S-T segment responses in presumably healthy subjects as having the same clinical significance. Ultimately we should be able to predict different degrees of risk for different subjects on the basis of multiple variables measured during and after exercise. There is certainly a growing body of evidence that this is true in the symptomatic population (Table II).[3–5,12–14] Erikssen et al.[15] found that an abnormal S-T segment response to exercise in the healthy subject was more likely the result of underlying coronary artery disease if the maximal heart rate and duration of exercise were less than predicted. Abnormal S-T segment depression at low exercise heart rates and work loads was also more prevalent among subjects with a true positive response. Finally, the subjects with abnormal coronary cineangiograms tended to demonstrate abnormal S-T depression in more than one electrocardiographic lead whereas subjects with a false positive response more often had S-T depression in one lead only. Erikssen et al. noted no differences in the prevalence rates of ventricular arrhythmias between subjects with true positive and false positive responses, but they did not correlate these arrhythmias with the exercise heart rates or work loads achieved.[12]

Other variables that may prove useful in differentiating the true positive from the false positive exercise response include an abnormal blood pressure response,[4] the magnitude of S-T depression and the postexercise duration of S-T depression.[13] It seems reasonable to assume that the healthy person who demonstrates mild to moderate degrees of S-T depression (2.0 mm or less) only at maximal or near maximal exercise is at a relatively low risk of a new coronary event, even if he has coronary artery disease, and he should be advised accordingly. On the other hand, the person who demonstrates a marked degreee of S-T segment depression at a low exercise heart rate or work load, and prolonged S-T depression after exercise is likely to be at much greater risk. Other abnormalities such as a progressive decrease in systolic blood pressure and complex ventricular arrhythmias should prove to be even more supportive in this respect (Fig. 1).

Implications of a positive exercise test in an asymptomatic person: Coronary cineangiographic studies may be warranted in some persons who demonstrate multiple abnormalities during exercise, but we emphasize that this fact has not yet been proved. As a general rule the physician should view an abnormal exercise test in a presumably healthy subject as a positive risk factor for future coronary heart disease. The magnitude of the subject's risk should be estimated by the physician according to the number of abnormal variables measured during the exercise test (Table II). The information gained from the exercise test should be utilized to motivate the subject to reduce or eliminate other potential risk factors such as hypertension, cigarette smoking, elevated blood lipid levels and mental stress. The opponents of this approach state that the physician should emphasize these preventive measures with all patients irrespective of the results of an exercise test. However, it is a reality of medical practice that the majority of patients require "hard" evidence to per-

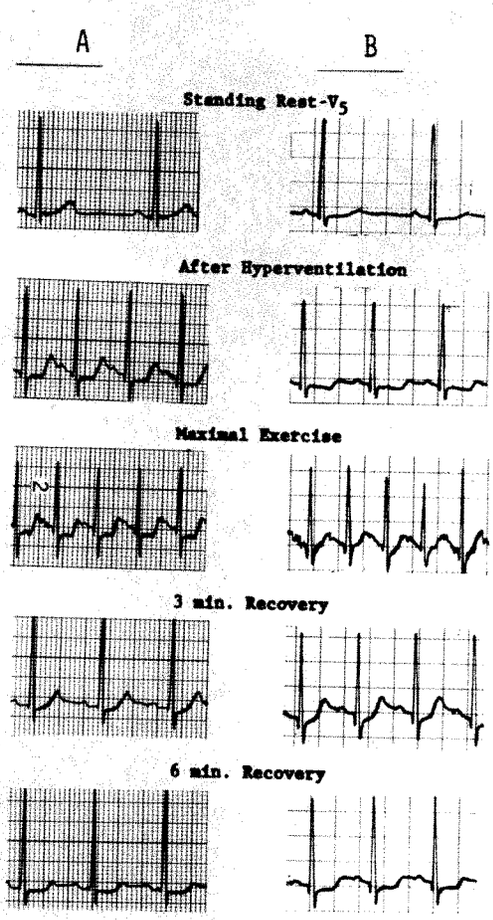


FIGURE 2. Types of S-T segment responses observed with exercise in two healthy subjects **(A)** and **(B)** demonstrating labile ST-T wave changes with standing hyperventilation. These subjects have remained free of symptomatic coronary artery disease during a mean follow-up period of 7 years.

suade them to modify their habits and life-styles. Furthermore, this approach allows the physican to concentrate his efforts on those subjects who will receive the greatest potential benefits.

Serial Exercise Testing of Presumably Healthy Subjects

Serial exercise testing of healthy persons who demonstrate an abnormal S-T segment response to exercise may prove to be a reliable means of identifying those subjects who are destined to have symptomatic coronary heart disease. For the past 10 years we have been following up with serial clinical and maximal exercise evaluations[4,12] more than 900 healthy men on the Indiana State Police Force. A brief review of our methods of handling the subjects who demonstrated an abnormal S-T segment response and of our results to date seems appropriate although the group is relatively small. The data are derived from the 47 presumably healthy subjects who demonstrated an abnormal S-T segment response during their initial evaluation at a mean age of 42 years. The exercise electrocardiographic data for each subject were submitted for computer averaging and quantitation of the S-T segment response.[16] In the absence of labile ST-T wave changes with hyperventilation, an S-T segment response was considered abnormal during exercise if the subject demonstrated 1.0 mm or more of S-T depression with a slope of 1.0 mv/sec or less. The postexercise S-T segment response was considered abnormal if there was 1.0 mm or more of S-T depression with a slope of 0.5 mv/sec or less. Fourteen subjects demonstrated an abnormal S-T segment response during exercise (and in some cases during the recovery period) and also demonstrated labile ST-T wave changes during standing hyperventilation (Fig. 2A). By study protocol design, these subjects were considered to have a false positive response. They were not informed that their exercise test results differed in any way from those of subjects who had a completely normal test. During a mean 7 year follow-up period there have been no new coronary events in those subjects. Of further interest, the majority of them have demonstrated S-T depression of a stable or a decreasing magnitude during serial testing.

Another subgroup of nine subjects had no abnormal S-T segment response during exercise but had abnormal S-T depression isolated to the 5 to 6 minute recovery period (Fig. 2B). One of these subjects had a new coronary event during the mean 7 year follow-up period. Unfortunately, he was the only subject from this subgroup who did not return for serial exercise testing after a 2 to 4 year interval, and he had an acute anterior myocardial infarction 5.5 years after his initial test. The remaining eight subjects have had at least one serial exercise test and in every case the magnitude of S-T segment depression has remained stable or decreased.

The remaining subgroup of 24 subjects had an abnormal S-T segment response during exercise but had no labile ST-T wave changes with standing hyperventilation. These subjects were informed that their response to exercise was abnormal and that this finding placed them at greater risk of having symptomatic coronary heart disease in the future. Each subject was given counsel concerning potential cardiac symptoms that he should report to his private physician or to one of the study physicians. Subjects who were overweight or who smoked were urged to eliminate these potential risk factors. None of the 24 subjects had hypertension at the time of their initial examination, but if hypertension was found during serial examinations the private physician was advised and therapy recommended. The private physicians were also informed of elevated lipid levels (cholesterol or triglycerides over 300 mg/100 ml). To date 10 of these 24 subjects have had a new coronary event. In seven the first new event was angina, and the subjects sought medical attention before a more complicating event such as a myocardial infarction occurred. Two of these subjects had their first episode of angina during serial exercise testing. In two other subjects a nonfatal myocardial infarction was the first event. One subject died suddenly during strenuous exercise; he had not reported new symptoms before his death. The two serial exercise tests performed by this

individual revealed that the S-T segment abnormalities had appeared progressively earlier in exercise, were of greater depth and had persisted longer in the recovery period. In 6 of the 10 subjects who had a new coronary event at least one serial exercise test was obtained before the new event. All 14 of the subjects who have remained asymptomatic have had at least one serial exercise test. The serial S-T segment responses of those who had a new event tended to demonstrate an earlier onset and a greater magnitude of S-T depression. Those who have remained asymptomatic tended to demonstrate stable or decreasing degrees of S-T depression. However, the differences between the two subgroups is not statistically significant because of the small number of subjects involved. (As stated previously, future studies may prove that aggressive intervention is indicated in such subjects even in the absence of symptoms.)

We believe that our approach to these presumably healthy subjects has been beneficial, and we have observed no adverse psychologic impact on the subjects in this select study group. On the basis of our experience to date we feel justified in handling the exercise test results of other healthy subjects who are studied in our laboratory in a similar manner.

Exercise Testing in Healthy Women

There have been very few epidemiologic studies of presumably healthy women who demonstrate an abnormal exercise stress test. There have been no coronary cineangiographic correlation studies of healthy women. The available data certainly suggest that the prevalence rate of false positive S-T segment responses with exercise is significantly greater in women than in men.[17–19] It remains to be seen whether useful information can be gained by selective exercise testing of potentially high risk subgroups of healthy female subjects. The value of other variables measured during exercise testing (Table II) must also be further investigated in the female population.

Summary

We believe that the exercise stress test is a very useful tool for detecting presumably healthy subjects who are at greater than expected risk of having symptomatic coronary artery disease. We do not advocate the use of exercise stress testing to screen the entire asymptomatic population. In general, exercise testing should be reserved for persons over the age of 45 years, especially for those with abnormalities that place them at greater than expected risk of symptomatic coronary heart disease. Persons with a very strong family history of coronary heart disease should be considered candidates for exercise stress testing, which may be advisable before the age of 45 years if there is a history of premature coronary heart disease and death. When an asymptomatic subject is screened with exercise stress testing, multiple variables in addition to the S-T segment response should be measured so that the physician can make an intelligent assessment of the subject's magnitude of risk for subsequent coronary heart disease. The information gained from the exercise test should be utilized to induce the healthy subject to modify his life-style and habits in the hope of reducing the risk of future symptomatic coronary heart disease. At the same time the subject should be educated to observe and promptly report early symptoms of ischemic heart disease. The value of serial exercise testing of asymptomatic subjects who demonstrate an abnormal S-T segment response is in need of further investigation.

Exercise Stress Testing in Symptomatic Persons

The keys to obtaining optimal diagnostic results from exercise stress testing of symptomatic patients are (1) proper patient selection, (2) use of proper techniques, and (3) an appreciation of the multiple, measurable variable that can be of diagnostic value even in the face of equivocal or normal S-T segment changes. In our opinion, an exercise stress test should never be performed for the sole purpose of obtaining a diagnostic exercise electrocardiogram. The physician should always quantitate the patient's exercise tolerance and he should measure those electrocardiographic, hemodynamic and performance variables that may assist him in identifying those patients who are potentially at greatest risk of major complications from coronary heart disease[8] (Table II). All the information obtained from an exercise stress test should be collated and utilized to arrive at a rational approach to medical management of the patient.

Proper Screening and Selection of Patients

Not all patients with suspected coronary heart disease are ideal candidates for *diagnostic* stress testing, and the number of such patients increases appreciably when the physician relies solely upon the presence of S-T segment abnormalities. Before performing an exercise test the monitoring physician should always strive to identify those patients who are prone to labile ST-T wave changes during *standing* hyperventilation. These patients tend to have an abnormal S-T segment response with exercise,[11] and the physician will be alerted to the possibility of a false positive response (Fig. 2). Additional variables such as the exercise tolerance time, the blood pressure response, rhythm disturbances and auscultatory changes must be recorded in these patients in an effort to differentiate a true positive from a false positive S-T segment response. The patient who cannot complete the second stage of the Bruce exercise protocol (or an equivalent work load with other exercise protocols) has a high probability of having significant heart disease.[3,5,20–21] If this reduction in work capacity is accompanied by a progressive decrease in systolic blood pressure[4] or complex ventricular arrhythmias[12,22] and a new clearly audible fourth sound gallop,[8] then the likelihood that coronary artery disease is the underlying cause of the S-T segment abnormalities during exercise is greatly enhanced. In patients who have fixed ST-T wave abnormalities at rest, intraventricular conduction defects or other clinical abnormalities that are known to give rise to false positive S-T segment responses, the physician must likewise rely on the measurement of nonelectrocardiographic variables.

Many previous studies designed to test the reliability of the exercise electrocardiogram in the diagnosis of coronary artery disease have included a significant number of patients who have patterns of myocardial infarction in the baseline 12 lead electrocardiogram. In our opinion this practice is inappropriate because these patients already have a confirmed diagnosis of coronary artery disease. To include such patients in a study of the diagnostic reliability of the exercise electrocardiogram will merely bias the results against the test. Several investigators have shown that the prevalence rate of abnormal S-T segment responses to exercise is lower in patients with a previous myocardial infarction.[23]

Exercise Techniques

The study of Erikssen et al.[10] confirms that patient selection and testing techniques can greatly influence the results obtained from exercise testing of a presumably healthy population. The results of a recent study by Chaitman et al.[20] emphasize the importance of these variables when studying symptomatic patients. They studied 100 consecutive men who presented with chest pain, a normal 12 lead electrocardiogram and no clinical history of myocardial infarction. The study was designed to test the differences in yield from the exercise electrocardiogram when different single and multiple lead systems are used. Their exercise electrocardiograms consisted of 14 simultaneously recorded leads. Coronary cineangiographic studies identified 66 patients who had significant coronary artery disease (stenoses of 70 percent or greater). Only 37 of 66 of these patients (56 percent) demonstrated an abnormal S-T segment response in a single unipolar V_5 lead. When single bipolar CC_5 or CM_5 leads were used to make the S-T segment interpretations, the yields increased to 43 of 66 (65 percent) and 45 of 68 (68 percent), respectively. When an 11 lead electrocardiogram (lead aVR excluded) was used to analyze the S-T segment response the yield increased to 50 of 66 (76 percent). A similar yield (77 percent) was obtained through the combined use of the CC_5 and CM_5 bipolar leads. When the authors looked at the standard 11 leads, the CC_5 and CM_5 leads and a vertically oriented bipolar (CL) lead, the number of abnormal S-T segment responses increased to 58 of 66 (88 percent). Further analysis of the authors' data reveals that 56 of the 58 (97 percent) abnormal responders were detected with a combination of three leads—unipolar V_3 and bipolar CC_5 and CM_5. These results reflect an obvious need for further studies to define the optimal number and placement of electrocardiographic leads for diagnostic exercise testing. They also make it apparent that previous study results casting doubt about the value of exercise testing for the diagnosis of coronary artery disease may have been misleading because less than optimal exercise testing techniques were used.

The results obtained from diagnostic exercise testing can also vary considerably depending upon the criteria used to define an abnormal S-T segment response. Most reported studies have used the conventional criteria of 1.0 mm or more of horizontal or downsloping S-T segment depression during or after exercise. Some investigators have reported that slow upsloping S-T segment criteria are of value in diagnostic exercise testing,[16,24] whereas others have argued that these criteria lead to an unacceptable number of false positive responses.[13] The studies of Erikssen et al.[10] and Chaitman et al.[20] strongly support the use of slow upsloping S-T segment criteria for diagnostic exercise testing. Erikssen et al. utilized the standard 12 lead electrocardiogram and multiple bipolar chest-head (CH) leads to analyze the S-T segment response during and after exercise. They reported that when unipolar leads are used to record the electrocardiogram *during* exercise a criterion of 1.0 mm or more of S-T depression at 0.08 second beyond the J point is just as reliable for diagnosing myocardial ischemia as the more conventional horizontal or downsloping S-T segment criteria. A criterion of 1.5 mm or more of slow upsloping S-T depression was found to be optimal with the bipolar leads. Erikssen et al. reported that the incidence of false positive responses was no greater with the slow upsloping criteria than with the conventional criteria. However, when the same slow upsloping criteria were applied to the electrocardiogram recorded *after* exercise there was a significantly greater incidence of false positive responses. This observation is in agreement with previous studies reported from our laboratory.[16,23]

Chaitman et al.[20] reported that a slow upsloping S-T segment criterion of 2.0 mm or more of depression at 0.08 second beyond the J point substantially increased the sensitivity of the exercise electrocardiogram in all leads studied except for the combined 14 lead system. With the 14 lead system they found that at least 1 lead always demonstrated horizontal or downsloping S-T depression. Chaitman et al. also reported that when a criterion of 2.0 mm or more of slow upsloping S-T depression was used there was no increase in the number of false positive responses in any lead system, and the criterion was equally reliable during and after exercise. These studies seem to confirm that slow upsloping S-T segment criteria will enhance the value of diagnostic exercise testing. However, the criteria used to define an abnormal S-T response will vary according to the lead system used[25] and according to whether the electrocardiogram is recorded during or after exercise.

Other Criteria for Diagnostic Exercise Testing

As mentioned, there are variables other than the S-T segment response that the physician should observe and measure during exercise testing (Table II). Some abnormalities, either alone or in combination, may be as diagnostic of coronary artery disease as an abnormal S-T segment response; and these abnormalities may occur in the absence of an abnormal S-T segment change.

Inverted U waves: Our laboratory is now carrying out a prospective study of the prevalence and significance of inverted or negative U waves during exercise stress testing (Fig. 3). We have found that approximately 5 percent of all patients who present with a history of chest pain and a normal 12 lead electrocardiogram manifest inverted U waves during or after ex-

ercise *without* accompanying S-T segment abnormalities. Although this prevalence rate is relatively small, careful observation for this abnormality will improve the diagnostic yield of the exercise test. In the absence of antiarrhythmic drugs or left ventricular hypertrophy, inverted U waves are highly specific for exercise-induced myocardial ischemia. To date we have observed negative or inverted U waves only in patients with lesions of the proximal left anterior descending coronary artery, with or without accompanying lesions in other coronary vessels. Inverted or negative U waves with exercise are probably overlooked in many laboratories for a number of reasons. First, they tend to occur as a transient phenomenon during peak exercise or in the immediate recovery period and they can be missed if electrocardiograms are not recorded at the appropriate times or are not free of noise and artifact. The inverted U waves may also be misinterpreted as terminal T wave inversion, especially when single left precordial leads are recorded. Inverted U waves are not usually seen in vertical lead systems and are usually reflected as prominent upright U waves in right precordial leads. Therefore, simultaneously recorded Y or Z axis leads will help to distinguish an inverted U wave from a negative T wave (Fig. 3). The diagnostic feature of negative U waves is a concave depression in the T-P segment that is below the isoelectric or P-Q segment (Fig. 3).

Abnormal systolic blood pressure responses: We recently studied the incidence and significance of decreases in systolic blood pressure during exercise testing.[4] Our results demonstrated that a sustained and progressive decrease in systolic blood pressure of greater than 10 mm Hg during graded exercise is virtually diagnostic of multiple vessel coronary artery disease provided the use of potent antihypertensive drugs, cardiomyopathy or advanced valvular heart disease are absent. The majority of our study patients who manifested an abnormal decrease in systolic blood pressure during exercise had previously documented coronary artery disease. In those who did not, the abnormal blood pressure response was usually accompanied by an abnormal S-T segment response. However, a few patients demonstrated a progressive decrease in systolic blood pressure during exercise without accompanying horizontal or downsloping S-T depression. When a decrease in systolic blood pressure is observed as an isolated finding during graded exercise testing, it is a more specific indicator than S-T segment abnormalities of underlying coronary artery disease.

Ventricular arrhythmias: Complex (multifocal or consecutive) ventricular arrhythmias or frequent (10/min or greater) ventricular premature complexes at exercise heart rates below 70 percent of the patient's predicted maximal heart rate are uncommon in the absence of underlying heart disease. However, these arrhythmias should not be used as the sole criterion for a diagnosis of coronary heart disease. If such arrhythmias are observed in conjunction with other abnormalities such as S-T depression, exercise-induced chest pain or a new S_4 gallop, then the combination of abnormalities becomes much more specific. Prolapse of the mitral value can produce a similar combination of abnormalities with the possible exception of a fourth sound gallop, but this diagnosis can usually be excluded in the absence of a mid systolic click or a late systolic murmur, or both. The combination of complex ventricular arrhythmias and a decreasing systolic blood pressure during exercise must be interpreted with caution unless the physician can confirm a sustained decrease in systolic blood pressure during time periods that are free of ventricular arrhythmias.[4]

Exercise Test as an Assessment of Severity of Coronary Disease and the Patient's Risk

Numerous studies have confirmed that the majority of false negative exercise tests occur in patients with

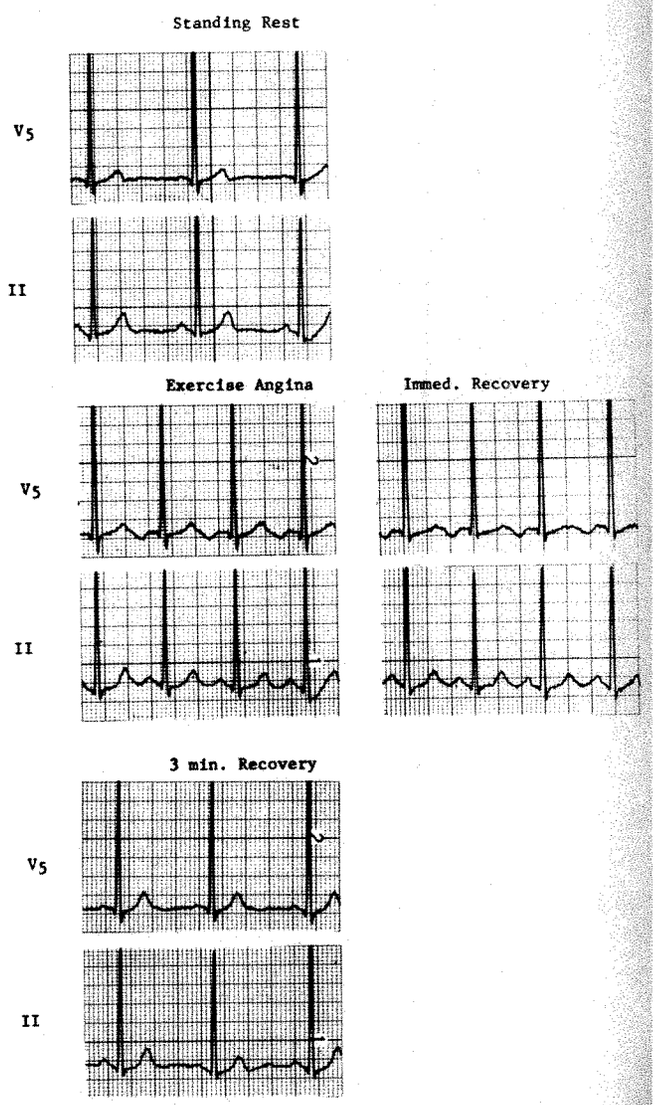


FIGURE 3. Inverted or negative U waves appearing at peak exercise and in the immediate (Immed.) recovery period in the absence of S-T segment abnormalities. The inverted U waves are present only in the bipolar V_5 lead and they are characterized by a downward deflection of the T-P segment below the baseline or P-Q segment. Coronary cineangiographic studies revealed a 90 percent stenosis in the proximal left anterior descending artery.

single vessel coronary disease,[5,13,16,20] and the greater the number of abnormal variables detected during the exercise test (Table II), the greater the probability that the patient has advanced multiple vessel coronary disease.[3–5,11–14,20] These observations are of great value in defining the patient's potential risk of having major complications from his disease. One hopes that they will ultimately prove of value to the physician in making decisions relative to appropriate medical and surgical management. Recent studies have shown a direct correlation between several abnormal exercise variables and subsequent risk for new coronary events or cardiac death.[3,5,21] McNeer et al.[3] reported that a combination of exercise variables can be both diagnostically and prognostically important in patients with known or suspected coronary heart disease. More than 97 percent of their patients who had an abnormal S-T segment response in stage I or II of the Bruce protocol had significant coronary artery disease, and more than 60 percent of these patients had three vessel disease. Advanced coronary artery disease was uncommon in patients who were able to complete three or more stages of the Bruce protocol without S-T segment abnormalities. A reduction in exercise capacity accompanied by S-T segment abnormalities also correlated significantly with a reduced survival rate. Similar correlations have been reported for all of the variables listed in Table II.

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Value and Limitations of the Electrocardiographic Response To Exercise in the Assessment of Patients With Coronary Artery Disease

Controversies in Cardiology—II

STEPHEN E. EPSTEIN, MD, FACC

Bethesda, Maryland

The results of exercise testing provide a probability statement rather than a definitive answer regarding the existence of coronary disease. Moreover, in *asymptomatic* subjects (1) the S-T segment response to exercise testing has a relatively poor predictive accuracy, (2) exercise testing does not appear to be a practical screening method for detecting subjects at high risk of sudden death, and (3) risk factors should be vigorously treated regardless of the results of screening studies for coronary artery disease. Hence, the probability statements derived from the electrocardiographic response to exercise testing do not appear to provide important enough diagnostic or prognostic information to justify routine use in asymptomatic subjects. Although exercise screening studies provide only marginal aid in detecting coronary artery disease in *symptomatic* patients, important *prognostic* information may be derived that could influence decisions regarding pharmacologic or surgical therapy. Thus, although electrocardiographic stress testing should not be used as a routine screening procedure, its judicious use in symptomatic patients may provide the physician with important information for patient management.

In recent years the reliability of the electrocardiographic response to exercise in detecting coronary artery disease, particularly in the asymptomatic subject, has been questioned.[1,2] This questioning was stimulated in large part by studies from two cardiac centers that have correlated, for the first time, the results of exercise stress testing with coronary angiography in asymptomatic subjects.[3–5] Because the ensuing reassessment of the role of exercise testing has led to important conceptual changes, this report reviews the data on the value and limitations of the electrocardiographic response to exercise testing as a noninvasive screening test for detecting coronary artery disease.

Predictive Accuracy

Symptomatic versus asymptomatic subjects: The predictive accuracy of the electrocardiographic response to exercise testing (Table I) is important clinically because it indicates what the chances are that a patient with a positive response actually has coronary artery disease. Figure 1, taken from the National Heart, Lung, and Blood Institute (NHLBI) study,[2,6] shows the predictive accuracy of the S-T segment response to exercise in patients who had typical angina pectoris or a history of prior myocardial infarction. In these symptomatic patients, the level of predictive accuracy was extremely high. There was only one false positive test, giving a predictive accuracy rate of 95 percent.

This result, typical of most previously reported studies, helped spawn the concept that the electrocardiographic response to exercise can be classified as "negative" or "positive" on the basis of S-T segment changes alone, and that the classification is highly reliable for identifying the presence of coronary disease in an individual patient. However, Figure 2 shows the results obtained in the *asymptomatic* subjects of the NHLBI study. Only one third of those

From the Cardiology Branch of the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received April 26, 1978; revised manuscript received June 27, 1978, accepted June 28, 1978.

Address for reprints: Stephen E. Epstein, MD, Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20014.

TABLE I

Glossary of Terms

Sensitivity = percent of all patients with disease who manifest an abnormal test

$$= \frac{TP}{TP + FN} \times 100.$$

False negative response = 100% − sensitivity.

Specificity = percent of negative results in subjects without the disease

$$= \frac{TN}{TN + FP} \times 100.$$

Predictive accuracy = percent of positive results that are true positive

$$= \frac{TP}{TP + FP} \times 100.$$

$$\text{Risk ratio} = \frac{\text{percent of subjects with a positive test who manifest coronary artery disease}}{\text{percent of subjects with negative test who manifest coronary artery disease}}.$$

FN = false negative; FP = false positive; TN = true negative; TP = true positive.

with a positive electrocardiographic response to exercise had 50 percent or greater coronary arterial narrowing on angiography; one third had normal coronary arteries and one third had slight luminal irregularities. Hence, approximately two thirds of the "positive" tests were falsely positive. This low level of predictive accuracy of the electrocardiographic response to exercise, when applied to asymptomatic persons, is very similar to the results obtained by Froelicher and his associates,[3,5] who also evaluated the test's reliability in asymptomatic subjects.

Dependency of predictive accuracy on disease prevalence: The apparent discrepancy between the high level of predictive accuracy of the exercise electrocardiogram in symptomatic patients versus the low level in asymptomatic subjects is merely a reflection of Bayes' theorem. This important theorem states that the predictive accuracy of any diagnostic test is directly related to the prevalence of disease in the population under study.

The curves illustrating the Bayesian theorem in Figure 3 were calculated assuming (1) test sensitivity and specificity levels of 95 percent (Table I), and (2) a sensitivity level of 75 percent and a specificity level of 85 percent. The curves show that the predictive accuracy of a positive exercise test *must* be extremely high among a subgroup of persons with a high prevalence rate of disease, such as patients with typical angina pectoris or a history of previous myocardial infarction. Because it was generally from such groups that previous investigators derived their study patients,[7–15] it was concluded that the electrocardiographic response to exercise testing has a high level of predictive accuracy. However, the curve also demonstrates that the level of predictive accuracy *must* be very low when an asymptomatic group—with a low prevalence rate of disease—is tested. This relation undoubtedly accounts for the low level of predictive accuracy of the electrocardiographic response to exercise for the asymptomatic subjects evaluated in the NHLBI[4,6] and Froelicher studies.[3,5] Figure 3 also shows the decrease in predictive accuracy when sensitivity and specificity levels are somewhat lower, particularly in a patient population with an intermediate prevalence rate of disease (10 to 40 percent), a rate that might be found in clinical practice.

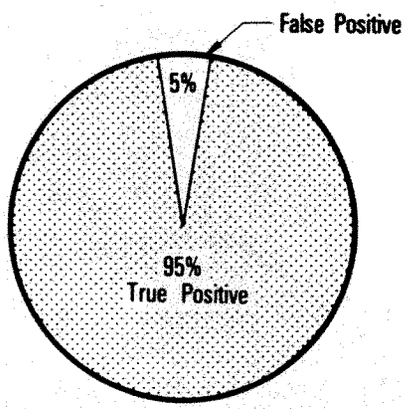


FIGURE 1. Predictive accuracy of 1 mm or greater S-T segment depression in response to exercise in 20 subjects with angina pectoris, myocardial infarction, or both.

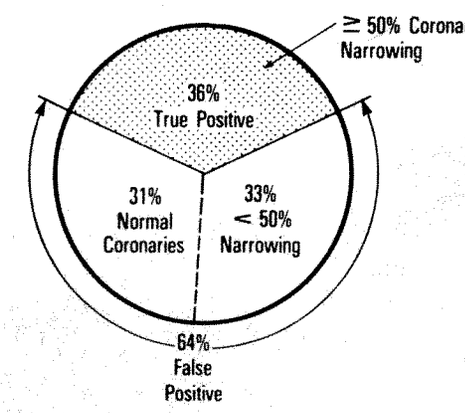


FIGURE 2. Predictive accuracy of 1 mm or greater S-T segment depression induced by exercise in 39 asymptomatic subjects.

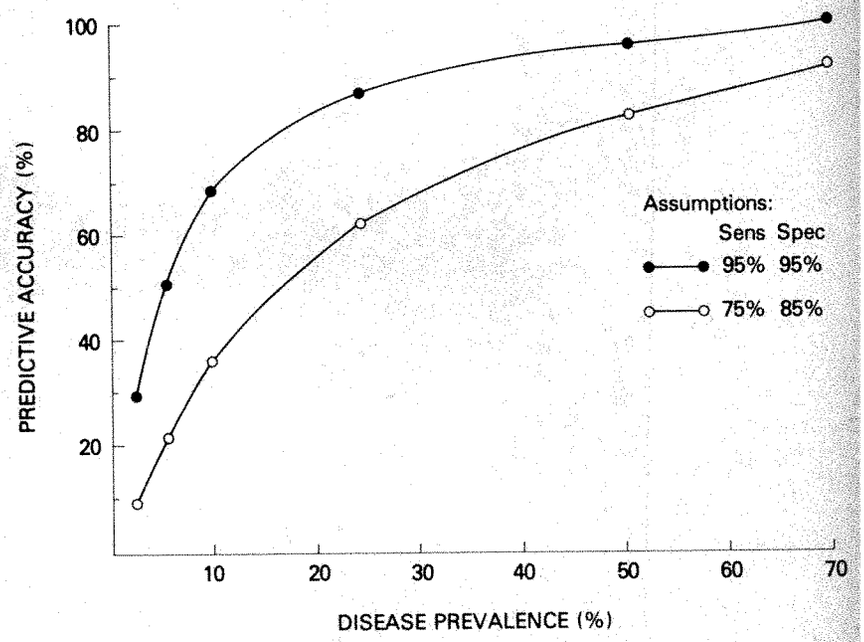


FIGURE 3. Influence of prevalence of disease, as well as sensitivity (sens) and specificity (spec), on the predictive accuracy of a positive test.

The simple calculations illustrated in Table II, based on the assumption that exercise testing has sensitivity and specificity levels of 95 percent, illustrate the dependency of predictive accuracy on the prevalence of disease. The calculations in Table IIA are based on a patient population with a 90 percent prevalence rate of coronary artery disease (a rate that might be found in an institution to which patients with symptoms of coronary disease are referred for possible operation). The level of predictive accuracy under such circumstances is very high. The calculations in Table IIB are based on a population with a disease prevalence rate of only 2 percent (a rate that might be found in an asymptomatic but otherwise unselected group, such as persons subjected to a routine electrocardiographic exercise test during an annual physical examination). Despite identical test sensitivity and specificity rates, the level of predictive accuracy in this group is very low.

TABLE II

Relation of Predictive Accuracy to Disease Prevalence

	Subjects (no.)		
	Total	With Positive Test	With Negative Test
A. Disease Prevalence Rate 90% (test 95% sensitive and 95% specific)			
Diseased	900	855	45
Nondiseased	100	5	95
Total	1,000	860	140
Predictive accuracy = 855/860 = 99%			
B. Disease Prevalence Rate 2% (test 95% sensitive and 95% specific)			
Diseased	20	19	1
Nondiseased	980	49	931
Total	1,000	68	932
Predictive accuracy = 19/68 = 28%			

Concept of continuum of risk: The low predictive accuracy of the S-T segment response to exercise demonstrated in these studies provoked much controversy,[16–18] from which emerged a more accurate understanding of the meaning and significance of the electrocardiographic response to exercise. It is now clear that changes in S-T segments during exercise stress testing do not provide a definitive answer regarding the presence of coronary artery disease but a probability

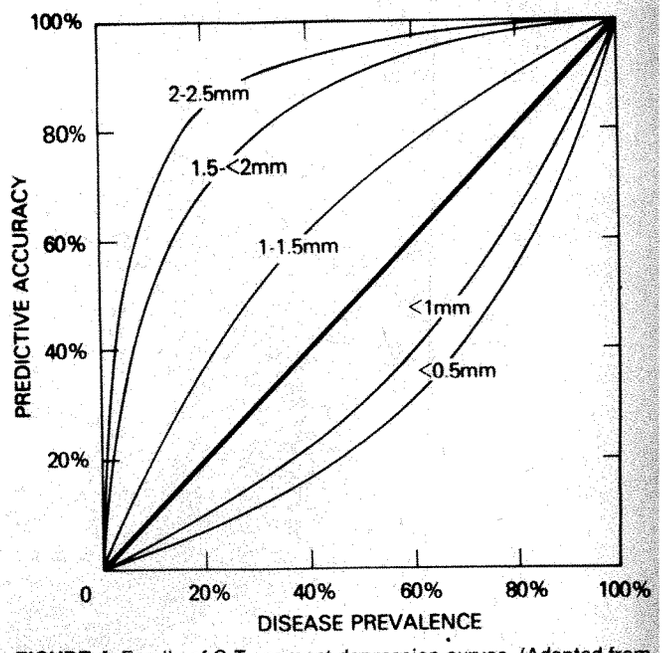


FIGURE 4. Family of S-T segment depression curves. (Adapted from Rifkin and Hood.[13])

statement based on the concept of a continuum of risk.

The concept of a continuum of risk was succinctly presented recently by Rifkin and Hood.[13] They analyzed the results of several previously published studies and constructed a family of predictive accuracy curves based on the degree of S-T segment depression. These curves (Fig. 4) demonstrate the naiveté of the concept that the S-T segment response to exercise can be simply classified as positive or negative; instead, there is a family of predictive accuracy curves, determined by both the degree of S-T segment displacement and the prevalence of disease in the population being studied. Thus, if a subject has 1 mm S-T segment depression and comes from a population with an estimated 20 percent prevalence rate of disease, that particular test result has a predictive accuracy rate of less than 40 percent. However, if the same person had 2 mm S-T segment depression, the probability of coronary artery disease would be high.

Figures 3 and 4 help clarify the diagnostic value and limitations of the S-T segment response to exercise in an asymptomatic population with a 10 percent or lower prevalence rate of disease. Only S-T segment depression of 2 mm or more could be considered highly predictive of coronary disease, and such a criterion will result in a very low sensitivity level because most asymptomatic patients with coronary disease will manifest less than 2 mm S-T segment depression during exercise. Conversely, even a mild degree of S-T segment depression is highly predictive of coronary disease in patients with angina or prior myocardial infarction, because this group of patients has a high prevalence rate of disease (greater than 90 percent). However, the need for such a test in this population is questionable because diagnosis is virtually certain on the basis of the patient's history.

Patients with atypical chest pain: Figures 3 and 4 also raise the question of whether the electrocardiographic response to exercise is of aid in establishing the presence or absence of coronary artery disease in patients with "atypical" chest pain. Figure 3 indicates that if the prevalence rate of disease in such a group is greater than 50 percent, then the rate of predictive accuracy would approach 80 to 90 percent; the rate of accuracy would be higher if 2 mm S-T segment depression were used to establish a positive diagnosis, and lower if 1 mm depression were used. However, the prevalence of disease in this group of patients is critically dependent on the rigidity of the criteria the physician uses to characterize chest pain as being possibly due to coronary artery disease. If the criteria are relatively rigid, then one would expect a high level of prevalence of disease, and therefore a high level of predictive accuracy. On the other hand, if the criteria lead to the inclusion of patients with less typical symptoms who are less likely to have coronary artery disease, then the levels of prevalence and therefore of predictive accuracy would be lower. Of note, the level of predictive accuracy in the NHLBI[6] and Detry studies[19] was relatively low in patients classified as having atypical angina pectoris.

Use of multiple risk variables to enhance predictive accuracy: Cohn et al.[20] also recognized that there was a continuum of risk for coronary artery disease given different exercise responses. They attempted to better quantify exercise responses and to enhance the predictive accuracy of the S-T segment response by using many risk variables in addition to S-T segment displacement. From their studies of 12 potential predictors of coronary artery disease, they found that the most important included the degree of S-T segment depression, configuration of the S-T segment, the patient's age and sex and the time of onset during exercise of S-T segment abnormalities. Weighting coefficients were calculated for each of these variables, and a treadmill score was determined for each patient. They found that the probability of coronary disease was directly related to the treadmill score: A high treadmill score indicated a high probability of coronary artery disease, a low treadmill score indicated a low probability of disease. However, attempts to categorize a treadmill score as "positive" or "negative" for coronary artery disease still revealed problems, even when a large number of risk variables were used in the analysis. Cohn et al. calculated that the particular variables used in their study would increase predictive accuracy by only 10 to 15 percent when compared with that obtained using S-T segment displacement alone.

Although this increase in predictive accuracy is small, attempts to enhance the reliability of the exercise test by using additional risk factors have merit. However, the key to increasing the predictive accuracy of electrocardiographic exercise testing rests on the possibility of identifying one or more risk predictors that have high independent predictive power. Detection of coronary calcifications by cardiac fluoroscopic examination illustrates this approach.

Cardiac fluoroscopy to detect coronary calcification: All patients entered into the NHLBI Type II Intervention Study underwent cardiac fluoroscopy to detect coronary calcifications in addition to exercise electrocardiographic stress testing. We found, in the asymptomatic population, that the identification of coronary calcifications had about the same predictive accuracy as exercise stress testing (35 to 40 percent) for identifying coronary artery disease producing 50 percent or greater narrowing.[6] However, 82 percent of persons with *both* a positive exercise response and coronary calcifications had coronary arterial narrowing of 50 percent or greater. Although the use of cardiac fluoroscopy considerably enhanced the predictive accuracy of exercise electrocardiography, sensitivity for detecting coronary disease diminished appreciably when identification of the disease required abnormality of both exercise and fluoroscopic tests.

Risk Ratio

Although a positive electrocardiographic response to exercise in an *individual* asymptomatic subject has little diagnostic value it does have important epidemiologic implications. Results of epidemiologic studies[21–23] demonstrate that a group of asymptomatic subjects with a positive electrocardiographic response is at higher risk

(10 to 15 times) for eventual development of coronary events than a group of asymptomatic subjects with a negative response. In other words, the risk ratio (Table I) is higher. However, this ratio should not be confused with predictive accuracy. Thus, although the risk ratio of a positive electrocardiographic response to exercise is high in asymptomatic subjects (10 to 15 times greater chance of having coronary artery disease), the predictive accuracy of the test is low (about 35 percent chance of having 50 percent or greater coronary stenosis). It is this latter application of the exercise test that relates most importantly to the diagnosis of coronary artery disease in the individual patient.

Sensitivity

The sensitivity rate of electrocardiographic exercise testing ranges from 40 to 95 percent.[4–15,19,21–23] The factors responsible for the varying sensitivity of the test include variations in the number of electrocardiographic leads,[24–27] the intensity of exercise utilized[21–23] and the magnitude of S-T segment depression required for a "positive" response. However, it also appears that the severity of the underlying coronary artery disease contributes importantly to the likelihood that a given patient will, or will not, manifest an abnormal S-T segment response to exercise.

Factor of disease severity: That disease severity may influence sensitivity is suggested by the results of studies demonstrating that the sensitivity of the exercise electrocardiogram is dependent upon anatomic severity of disease, as judged from the number of vessels narrowed.[8,9,14,27] Thus, Bartel et al.[14] demonstrated that in symptomatic patients 1 mm or greater S-T segment depression was found in 40 percent of those with single vessel disease, 66 percent of those with double vessel disease and 76 percent of those with triple vessel disease. In addition, McHenry[28] found that sensitivity of the exercise electrocardiogram is greater in patients who had angina during the exercise test (83 percent) than in patients who did not (50 percent). Finally, several studies have evaluated sensitivity of the electrocardiographic response for detecting coronary artery disease in asymptomatic subjects.[21–23] Sensitivity ranged from 58 to 66 percent, a figure generally lower than that usually attained in studies of symptomatic patients using graded exercise stress.[5,8,9,19,24]

It therefore appears that, like predictive accuracy, the sensitivity of the electrocardiographic response to exercise is dependent upon the particular patient population studied, and that if an asymptomatic or minimally symptomatic group is being evaluated, the test can be expected to be less sensitive than it is in patients with more severe symptoms.

Cost-Effectiveness of Using Exercise Testing to Detect and Treat Asymptomatic Patients With Coronary Artery Disease

One of the most common justifications for use of the exercise electrocardiogram as a screen for coronary disease is that a positive electrocardiographic stress test identifies patients who have a high probability of underlying coronary artery disease and who therefore should have aggressive treatment of risk factors.[16] If this philosophy were applied in an egalitarian fashion, the financial impact on the country's health budget would be staggering. There are more than 30 million asymptomatic men in the United States between 40 and 65 years of age. If a stress test costs $100, the total cost for screening this population would be $3 billion. Once this enormous expense is considered, it is only reasonable to inquire whether therapeutically useful information will be gained and whether the information is worth the price.

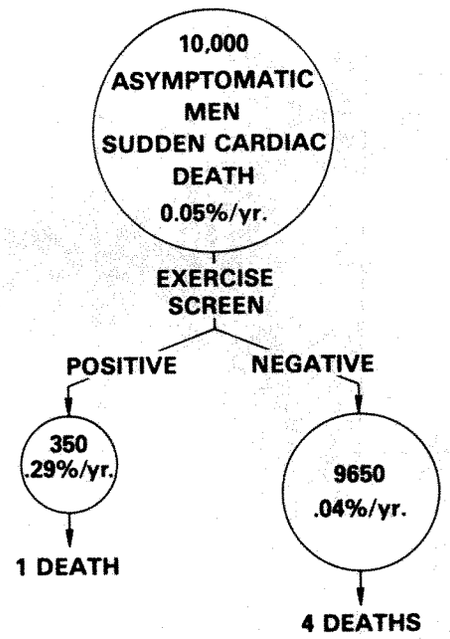


FIGURE 5. Practical implications of using an exercise screening test to identify asymptomatic subjects at risk of sudden death.

If the results are intended to provide the stimulus for more vigorous treatment of risk factors, I think the answer to these questions must be "no." Aggressive treatment of risk factors should be pursued in all subjects, regardless of the results of exercise stress testing. This approach seems appropriate because subjects who are free of disease at the time of testing may experience disease in the future and because many patients with underlying coronary artery disease have negative stress tests.

Identification of asymptomatic subjects at high risk of sudden death: Another justification for using the electrocardiographic response to exercise testing to screen asymptomatic subjects stems from the finding that sudden death is the first manifestation of coronary artery disease in about 5 to 10 percent of patients.[29] A positive exercise test, by identifying this high risk group, would allow preventive treatment to be instituted.[30] However, the practical aspects of such a screening study must be more carefully considered. In the Seattle Heart Watch Study, Bruce and co-workers[29] found that among 2,760 men initially free of heart disease, the incidence rate of sudden cardiac death was only 0.05 percent/year. Maximal exercise testing identified 3.5 percent of the

population with 7 times greater risk of *any* coronary heart disease event (angina, myocardial infarction or death). Although comparable data relating to sudden death *as such* are lacking, as a very rough approximation one can assume exercise testing can similarly identify a subgroup specifically at risk of sudden death. Figure 5 demonstrates the practical implications of using an exercise screen to identify *one* asymptomatic subject at risk of sudden death over the course of 1 year. Employing assumptions derived from the incidence of new coronary events in the Seattle Heart Watch Study,[29] 10,000 asymptomatic men, with an annual mortality rate of 0.05 percent/year, would have to undergo exercise screening. The exercise screening test would yield a group of 350 men (3.5 percent of the population) with a risk of sudden death 7 times that of the remainder of the population. In this group of 350 men, 1 will be destined to die (0.29 percent/year annual mortality).

But, how can this 1 subject be selected out from the remaining 349 who will not die? Clearly, there must be an answer to this question if such a screening approach can be translated into therapeutic action because it would be medically unwise to institute aggressive treatment for a group of persons, of whom 99.7 percent are not at risk of sudden death. Thus, before a therapeutic intervention can be initiated, additional screening would be required to better identify the one patient who will die. Should each of the 350 subjects in the "high" risk subgroup have coronary angiography? Would 24 hour electrocardiographic monitoring or radionuclide studies provide helpful information?

Although the answers to these questions are not yet available, the questions themselves point to the impracticality of the approach. If one assumes that the cost of an exercise screening study is $100, it would cost $1 million (10,000 × $100) to identify a high risk subgroup containing one subject who will die in the next year. Because this subgroup has such a low rate of coronary events, additional screening studies (requiring additional hundreds of thousands of dollars) would have to be carried out. Even if this approach were successful, the much larger low risk subgroup would contain four (or 80 percent) of the patients destined to die, none of whom would have been so identified by screening studies. Thus, until more effective screening studies are available for an asymptomatic population, it would be impractical to think of using exercise testing for the purpose of preventing sudden coronary death in this group.

Use of Exercise Stress Testing to Detect Symptomatic Patients at High Risk of Sudden Death

Although detection of a high risk asymptomatic subgroup with exercise screening studies appears impractical it is possible that a particular exercise response can help identify a subgroup of patients with known coronary disease whose risk of sudden death is great enough to warrant consideration of coronary bypass surgery. For example, the Seattle Heart Watch Study[29,31] developed data that allow identification of a very small subgroup at high risk of dying. Of note, the patients in this high risk subgroup had an enlarged heart and greatly impaired exercise capacity. In addition, McNeer et al.[15] recently demonstrated an approximately 10 percent annual mortality rate for patients with coronary artery disease who, during exercise stress testing, had S-T segment depression of 1 mm or more during either stage I or II of the Bruce exercise protocol, or at a low heart rate during exercise. However, the patients studied were severely symptomatic; 56 percent could reach only stage I or II of the exercise protocol before stopping, and more than 40 percent of these had "unstable angina."

These studies point to an important potential application of exercise testing that may eventually provide one of the most vital justifications for its use. However, at present most subjects identified as being at high risk are patients who would be considered surgical candidates on the basis of symptomatic limitation. The challenge that remains is to identify patients with coronary artery disease who are at high risk of sudden death, but whose symptoms are sufficiently mild that they would not be considered surgical candidates on the basis of severe functional limitation.

Patients after myocardial infarction: Intensive investigational efforts also are being directed toward the early postmyocardial infarction period. Mortality within the first 6 months after discharge from the hospital is relatively high, and it is possible that information obtained during exercise testing, perhaps in conjunction with ambulatory electrocardiographic monitoring, can help identify a high risk subgroup that might benefit from more aggressive pharmacologic treatment or from operative therapy.

Patients with left main coronary arterial narrowing: These patients present another challenge. If it is considered that all such patients who are symptomatic should be operated on[32] it becomes essential to develop a screening test that helps identify patients with this abnormality. The alternative is to subject all patients with symptomatic disease to cardiac catheterization. At present no variable or group of variables derived from exercise stress testing can distinguish the patient with left main coronary artery disease from the patient with significant narrowing of two or three coronary arteries. Nonetheless, it may ultimately prove possible to identify a subgroup containing a relatively high percent of patients with narrowing of the left main coronary artery.

In this regard, McNeer et al.[15] found that about 25 percent of patients who had 1 mm or greater S-T segment depression during relatively mild exercise (stage I or stage II of the Bruce protocol) had 50 percent or greater narrowing of the left main coronary artery. A similar proportion of patients with 2 mm S-T segment depression during graded exercise treadmill testing had significant narrowing of the left main coronary artery.[14] Unfortunately, the majority of patients in these studies were severely symptomatic, thus raising the question of whether such results are applicable to patients who

have mild symptoms and who are therefore not surgical candidates because they do not have a greatly restricted lifestyle.

Information pertinent to this important question has been obtained from a recent investigation (unpublished observations[33,34]) in which we studied 156 mildly symptomatic patients with coronary artery disease. Exercise was terminated at 85 percent of predicted maximal heart rate or at the onset of symptoms, whichever appeared first. Although 10 percent of the total group had 50 percent or greater narrowing of the left main coronary artery, about 20 percent of the subgroup of patients that had 1 mm or greater S-T segment depression during or after exercise had left main coronary artery disease. And less than 10 percent of patients with such disease failed to manifest at least 1 mm S-T segment depression. If these results are substantiated by additional studies, a strong case can be marshalled for using exercise screening to identify persons for angiographic study. Such a screening process would reduce the demand on angiographic facilities and would help identify patients whose survival may be enhanced by operative intervention.[32]

Other Uses of Exercise Testing

Detection of cardiac arrhythmias: Exercise testing can elicit arrhythmias that otherwise might go undetected.[35] The demonstration of such arrhythmias may provide the physician with information explaining unusual exercise-related symptoms or may provide the evidence pointing toward more intensive and specific antiarrhythmic therapy.

Evaluation of origin and severity of symptoms: Observation of the patient during exercise can also be extremely valuable, particularly when an accurate history is difficult to obtain. Symptoms might develop that clarify an otherwise ambiguous clinical situation. On occasion, noncardiac complaints can be properly identified. Such a noncardiac origin of symptoms may go unrecognized if reliance is placed on history alone.

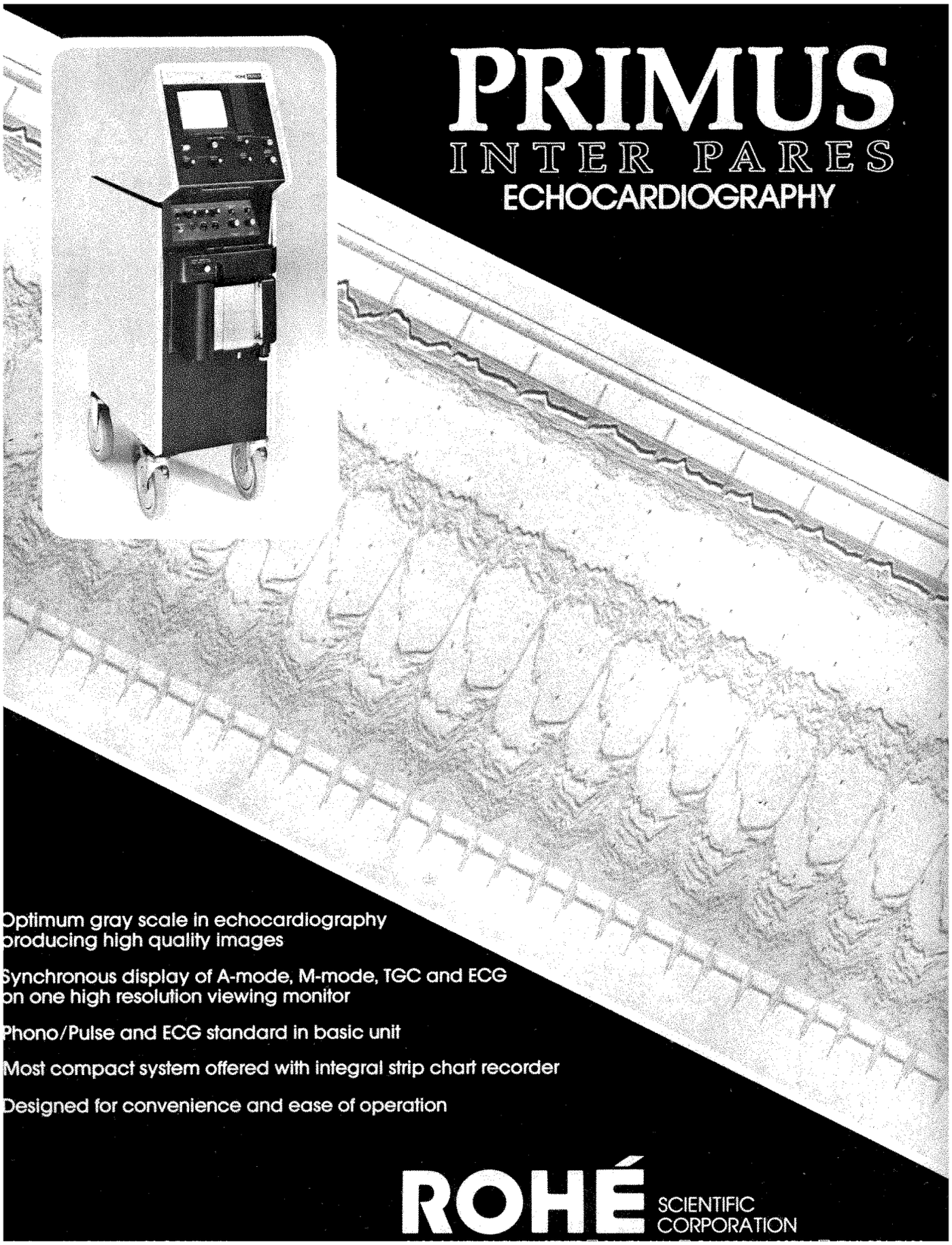
In addition, some patients are stoical, and the precise degree of symptomatic limitation may be grossly underestimated. The development of angina at a very early stage of exercise may considerably enhance understanding of the patient's clinical status and might even importantly influence therapeutic decisions.

Application to specific occupational groups: Finally, an epidemiologic approach to the statistical likelihood of an asymptomatic subject having disease might be justified in certain occupational groups. For example, a cogent case can be made for routine exercise stress testing for airline pilots, whose risk of sudden death might have a catastrophic outcome for many others. Thus, although it might be inappropriate to conduct coronary angiographic studies in all asymptomatic persons with a positive electrocardiographic stress test, such invasive studies might be justified for persons in special occupations.

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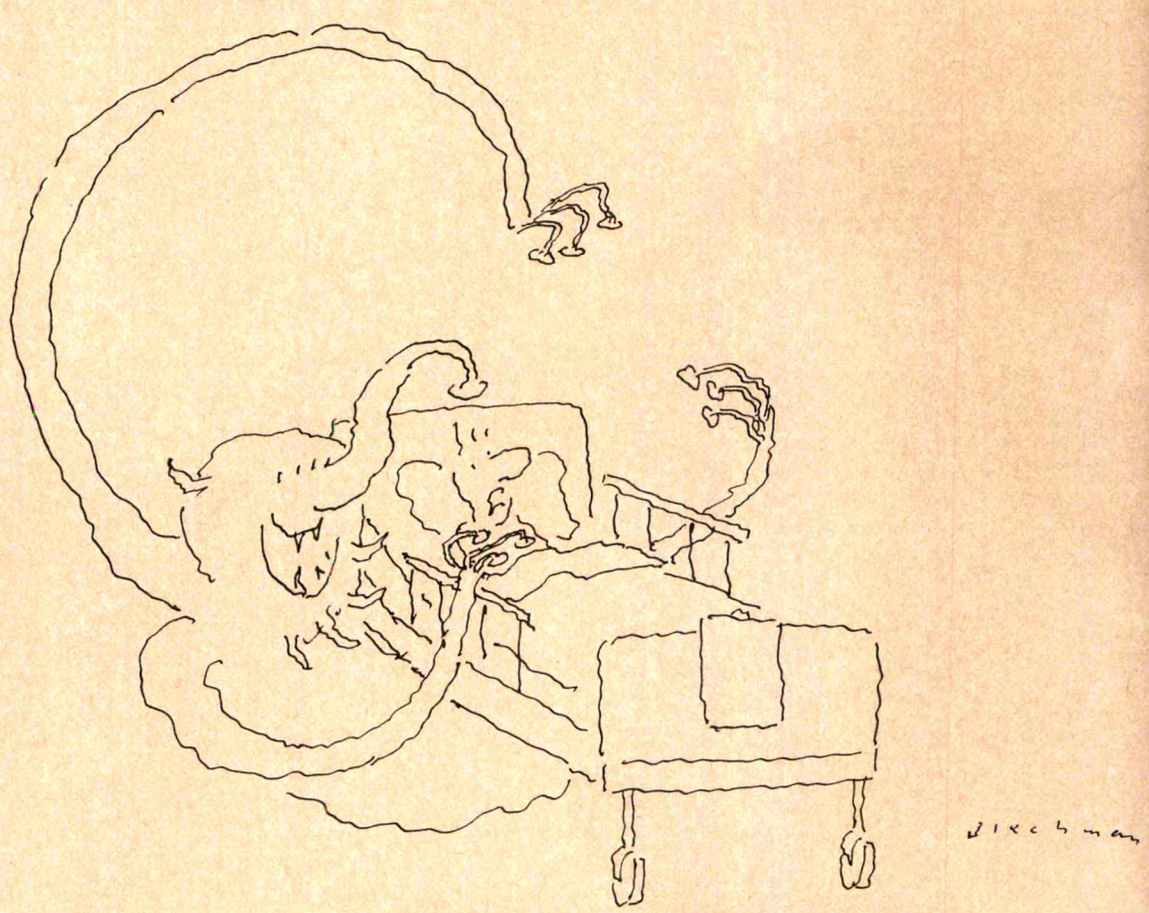
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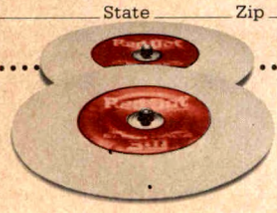
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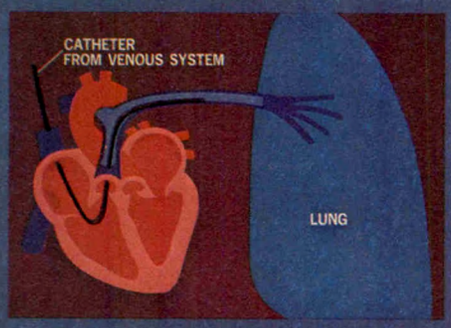


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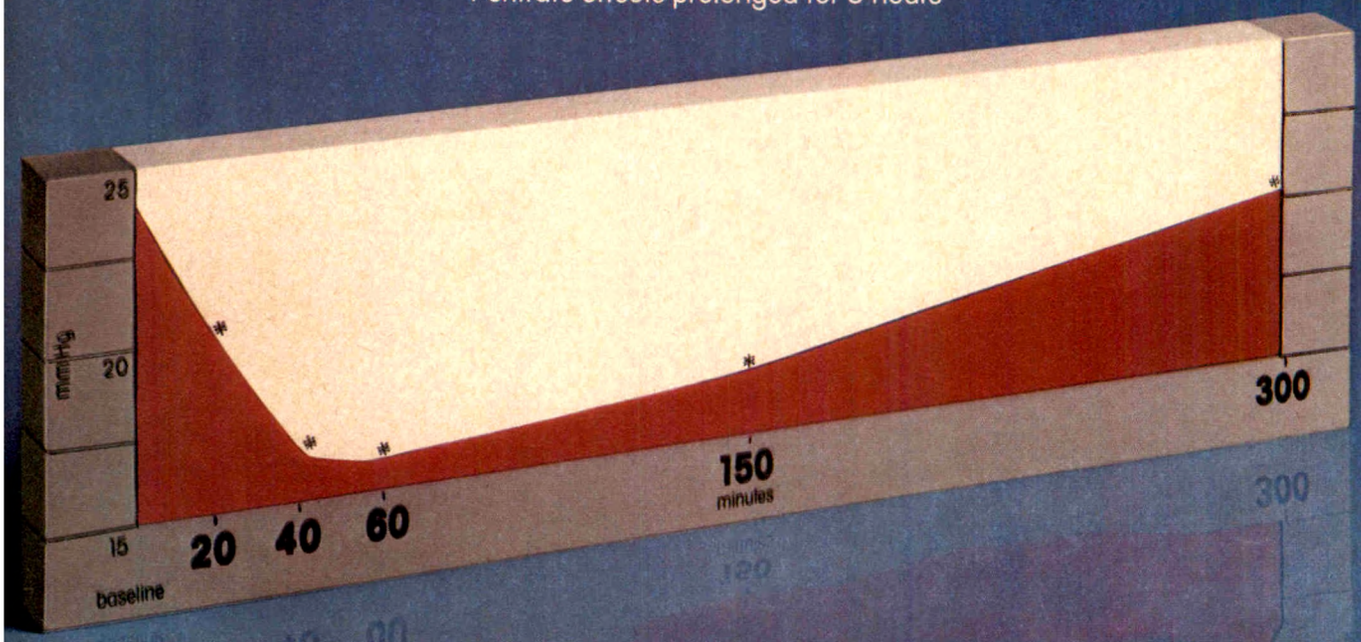
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1. Klein RC, Amsterdam EA, Pratt C, et al: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy. Presented at The American Federation for Clinical Research, San Francisco, Calif, April 29-May 1, 1978.

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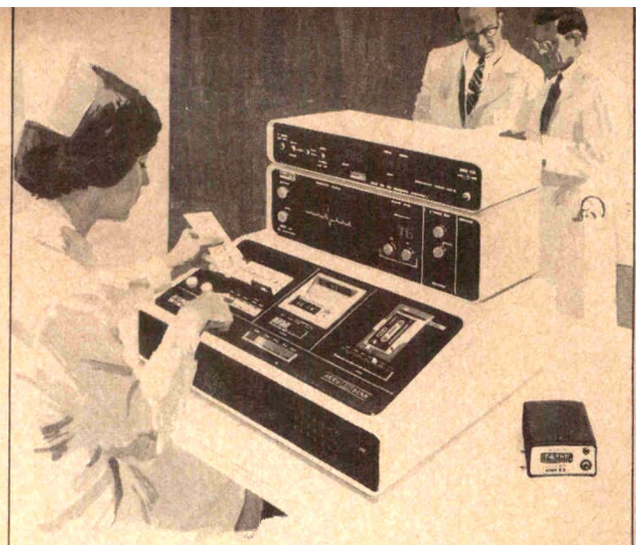
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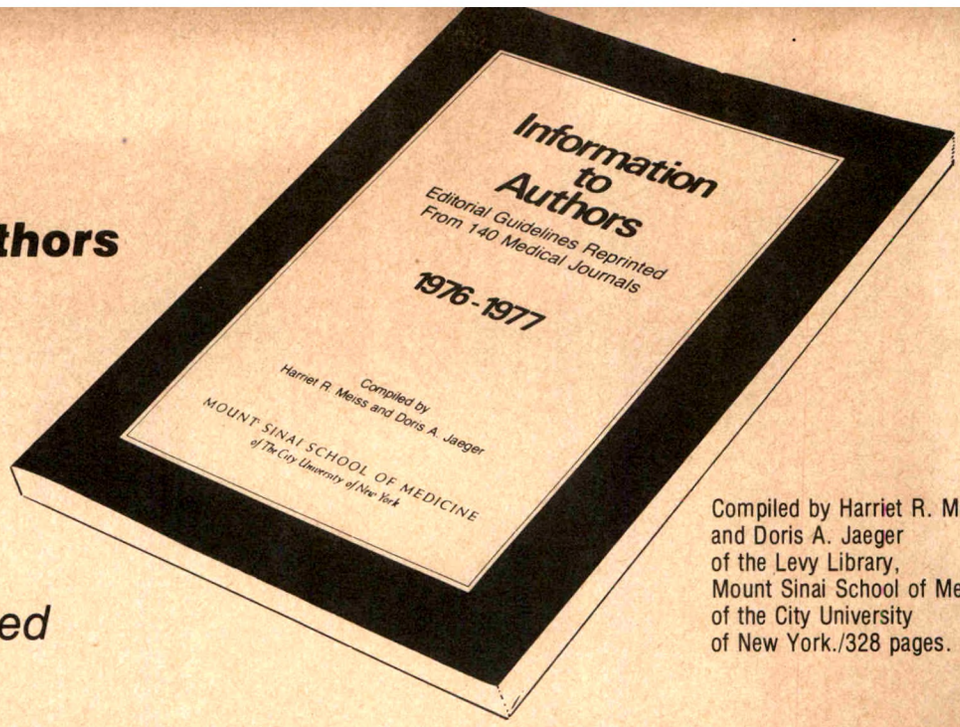
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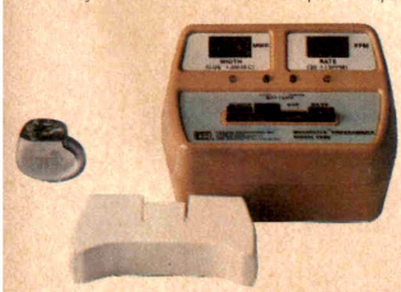
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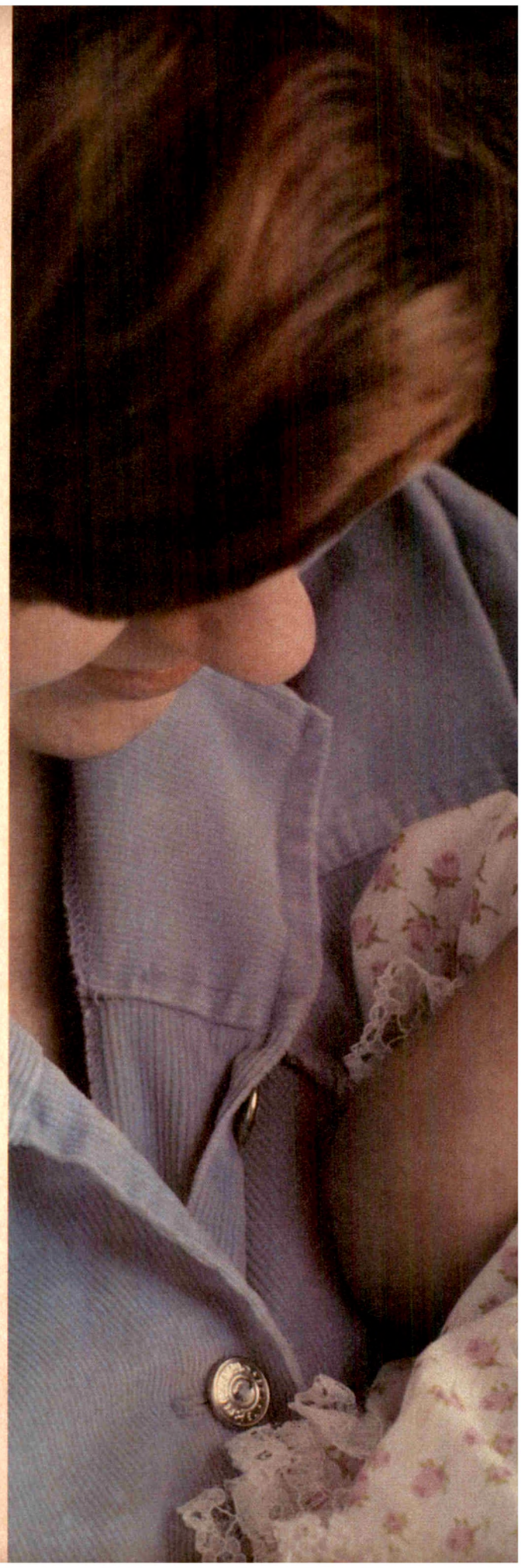
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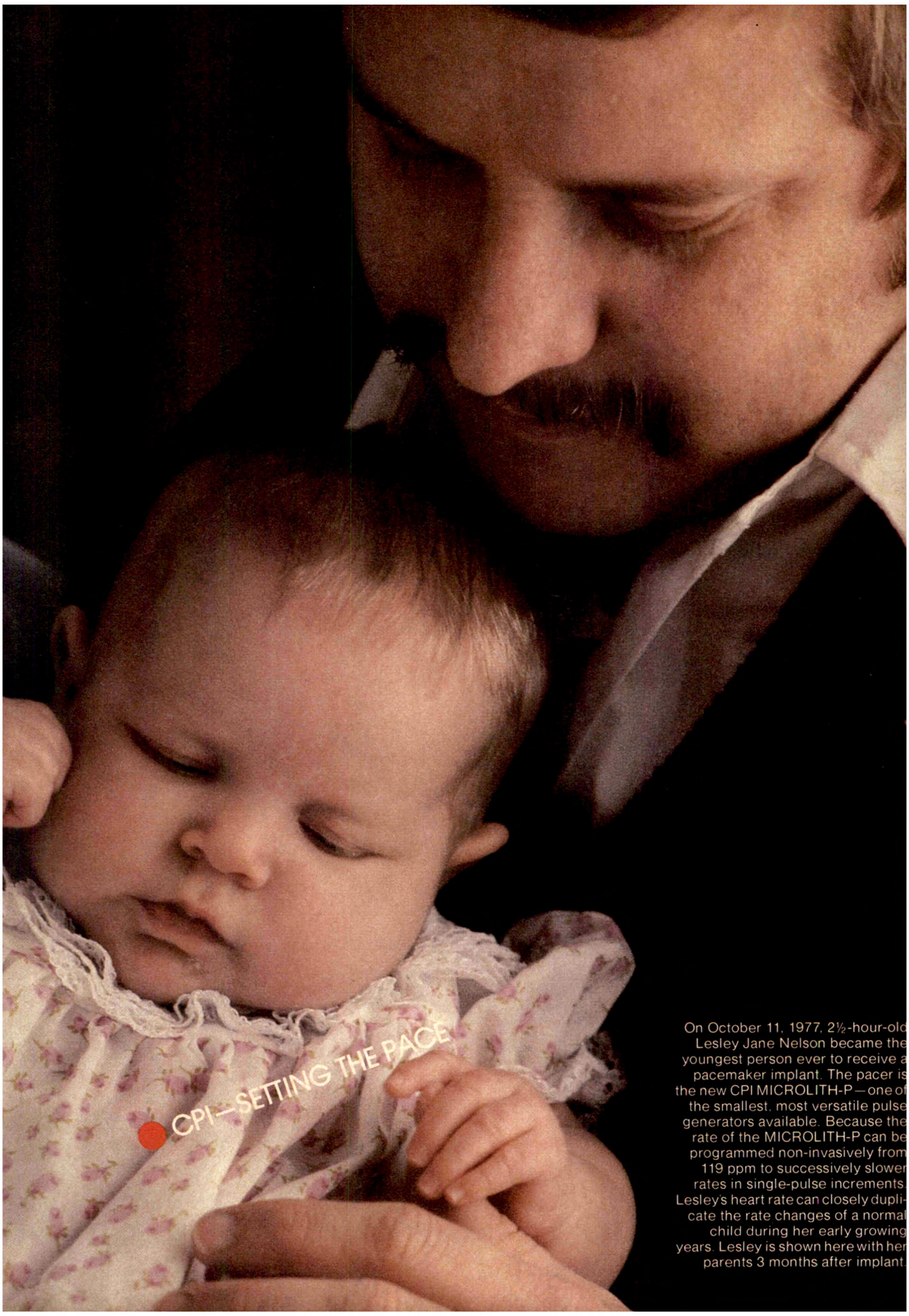


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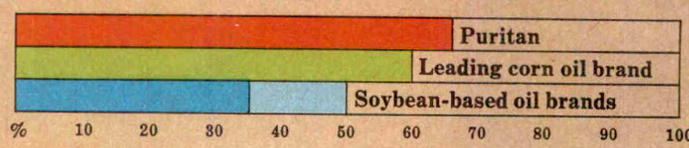
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Reference: 1. Witchi, J.C. et al., *J. Am. Dietetic Assoc. 72:* 384, 1978.

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Thallium-201 Myocardial Imaging in Anomalous Left Coronary Artery Arising From the Pulmonary Artery

Applications Before and After Medical and Surgical Treatment

JOHN P. FINLEY, MD, CM
ROBERT HOWMAN-GILES, MB, BS
DAVID L. GILDAY, MD, CM
PETER M. OLLEY, MB, BS
RICHARD D. ROWE, MD, ChB

Toronto, Ontario, Canada

Thallium-201 myocardial imaging was performed on six patients with an anomalous left coronary artery arising from the pulmonary artery. Initial images in three children (aged 4 months, 12 months and 2 1/2 years, respectively) demonstrated anterolateral perfusion defects in agreement with the electrocardiographic localization of infarction. Repeat imaging in two patients 2 to 3 months later, after clinical improvement with anticongestive therapy, demonstrated a reduction in the perfusion defect. In 3 other patients (aged 16, 16 and 20 years, respectively) thallium-201 scans performed during exercise stress demonstrated normal myocardial perfusion 7 to 15 years after operation (ligation of anomalous left coronary in two, ligation plus bypass graft in one).

Thallium-201 imaging appears to be helpful in monitoring changes in myocardial perfusion before and after medical or surgical treatment of an anomalous left coronary artery, and may shed light on the pathophysiology of the defect. A possible practical limitation of thallium-201 imaging in this condition is the difficulty of imaging subendocardial infarction.

An anomalous left coronary artery arising from the pulmonary artery represents 0.24 percent of cases of congenital heart defects seen in a large referral center.[1] Although the condition produces myocardial ischemia and infarction at an early age, the indications for medical and surgical treatment are currently under debate[2–9] and therapeutic decisions are rendered difficult by incomplete knowledge of the disease process. Clearly, a technique that would allow accurate evaluation of myocardial perfusion in various stages of the development of the anomalous artery would facilitate both understanding and treatment of the defect. This paper describes the use of thallium-201 imaging, a technique widely used to assess myocardial ischemia and infarction in adults,[10–12] in children before, during and after treatment of anomalous left coronary artery.

Patients and Methods

Patients: Between January 1955 and December 1976, a total of 22 patients with an anomalous left coronary artery were seen at this institution. The diagnosis was confirmed with findings at one or more of the following procedures: cardiac catheterization, surgery or autopsy. Of the 22 patients, 13 died, 8 are still alive and 1 is lost to follow-up. This report concerns six of the living patients available locally for follow-up. Three of the six (aged 4 months, 12 months and 2 1/2 years, respectively) were treated medically; three (aged 16, 16 and 20 years, respectively) had undergone cardiac surgery because of the anomalous left coronary artery.

From the Divisions of Cardiology and Nuclear Medicine, Departments of Pediatrics and Radiology, The Hospital for Sick Children, Toronto, Ontario, Canada. This study was supported in part by the Ontario Heart Foundation, Toronto, Canada. Manuscript received March 8, 1978; revised manuscript received May 9, 1978, accepted May 10, 1978.

Address for reprints: Richard D. Rowe, MD, Division of Cardiology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

TABLE I

Clinical Findings in Six Patients With Anomalous Left Coronary Artery Arising From Pulmonary Artery

Case no.	Sex	Age (yr) At Onset of Symptoms	Age (yr) On First Visit	Chest X-Ray	Rest ECG	Cath	Surgery Type	Surgery Age (yr)	Interval to Postop Cath (yr)	Age (yr)	Present Status Clinical	Present Status ECG Rest	Present Status ECG Ex	Present Status Scan
1	F	2/12	3/12	+	+	+	0	. . .	. . .	7/12	CHF	+	0	+
2	F	6/12	11/12	+	+	+	0	. . .	. . .	1 3/12	CHF	+	0	+
3	M	10/12	11/12	+	+	+	0	. . .	. . .	2 1/2	CHF	+	0	+
4	M	1/12	3/12	+	+	0	Ligation	4/12	0	16	Well	N	+	N
5	F	4/12	10/12	+	+	+	Ligation	6	1/12	20	Well	N	+	N
6	F	None	9	N	+	+	Graft	9	1;6	16	Well	N	N	N

+ = abnormal; 0 = not done.
Cath = cardiac catheterization; CHF = congestive heart failure; ECG = electrocardiogram; Ex = exercise; N = normal; Postop = postoperative.

All six patients were being followed up in the cardiology outpatient clinic and underwent physical assessment and chest X-ray examination and an electrocardiogram obtained at rest. The three older patients (postoperative group) had an exercise electrocardiogram, using a bicycle ergometer according to the work load schedule of Goldberg et al.[13] with continuous direct electrocardiographic monitoring. The end point of the test for each patient was marked fatigue.

Thallium-201 myocardial scans: These were performed with the radionuclide injected at maximal stress during exercise electrocardiography in the three older patients, and at rest in the other three. Myocardial images were obtained with a high resolution gamma camera (Picker Dyna camera 4/15) and covering collimator, within 10 minutes of an intravenous injection of 1.15 mCi/m^2 body surface area of thallium-201 chloride (New England Nuclear Corporation, Billerica, Massachusetts). The projections recorded were anterior, 20°, 45° and 60° left anterior oblique, with imaging to a level of 750 counts/cm^2 over the left ventricular muscle, with a 20 percent window set symmetrically around the 69 to 80 Kev X-ray peak. The camera was interfaced to a Medical Data Systems Computer for later analysis of the images. The whole body radiation dose absorbed from thallium-201 in adults[14] is 0.21 rads/mCi; for the testes and kidneys it is 0.59 and 1.17 rads/mCi, respectively.

For stress imaging, an intravenous line was started before exercise. The thallium-201 was injected at peak exercise or when exhaustion appeared imminent. The patients were then encouraged to exercise for a further 30 to 60 seconds to facilitate maximal clearance of tracer from the blood. After com-

TABLE II

Angiographic Findings in Six Patients With Anomalous Left Coronary Artery From Pulmonary Artery

Case no.	Age (yr)	Q_p/Q_s	Right Coronary Artery	Collateral Vessels Visualized	Left Coronary Artery	Left Atrium	Left Ventricle	Other
1	3/12	1.3	Dominant, dilated	Yes; proximal and distal collateral vessels	Normal	Enlarged	Dilated, poor contraction	Marked mitral insufficiency
2	3/12	1.0	Dominant, dilated	Yes; proximal and distal collateral vessels	Small	Enlarged	Dilated, poor contraction	Mitral insufficiency
3	1 1/2	1.4	Dominant, dilated, tortuous	Yes; early conal shunt	Small, branches normal	Normal	Dilated, poor contraction, noncontracting apex and anterolateral area	Normal levophase
4*		. . .	. . .	. . .	. . .	. . .	. . .	. . .
5†	6	1.8	Dilated	Yes	Dominant, dilated	Enlarged	Dilated, poor contraction	
	6‡		Smaller	Yes	Smaller	. . .	NV. . .	Mild aortic insufficiency, no residual shunt
6	9	2.1	Dominant, dilated	Yes	Dilated	Normal	Normal, good function	Mild aortic insufficiency
	10‡		Dilated		Dilated	NV. . .	NV. . .	Aortogram, graft patent, mild aortic insufficiency
	16‡		Dilated	Yes	Dilated	Normal	Normal size and function	Graft patent, prolapse right coronary cusp, mitral valve normal

* Cardiac catheterization not performed.
† Aortogram at age 10 months demonstrated only a right coronary artery.
‡ Postoperative study.
NV = not visualized; Q_p/Q_s = pulmonary to systemic flow ratio.

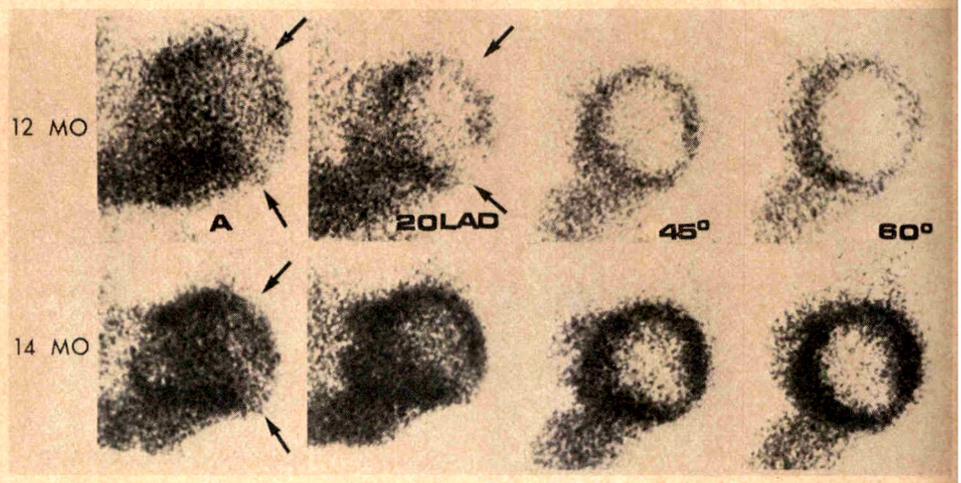


FIGURE 1. Case 2. Thallium-201 scans from a medically treated infant with anomalous left coronary in anterior and 20°, 45° and 60° left anterior oblique (LAO) views. **Arrows** indicate perfusion defect.

pletion of exercise, the patient was allowed to rest until the heart rate returned to normal. Imaging was performed about 10 minutes after injection.

Results

Patients Not Operated On (Cases 1 to 3)

All three patients had been symptomatic since the early months of life, and all had the typical findings of congestive heart failure, cardiomegaly on chest X-ray film and an electrocardiogram with a deep Q wave in leads I and aVL and inverted T waves in the left chest leads, suggesting anterolateral infarction (Table I).

Cardiac catheterization at the time of diagnosis demonstrated normal pressures with minimal or no rise in oxygen saturation at the level of the main pulmonary artery. Cineangiography revealed a dilated and dominant right coronary artery, good collateral vessels at proximal and distal levels, a normal or small left coronary artery and impaired left ventricular function, with mitral insufficiency in two cases (Table II).

Treatment with digoxin successfully controlled the congestive failure in these patients, who were last seen at age 7 months, 15 months and 2 1/2 years, respectively. In each, the chest X-ray film continued to show cardiomegaly, and the electrocardiogram was unchanged (Table I).

Thallium-201 myocardial scans at rest: These were abnormal. In Case 1, on initial study, there was an area of decreased tracer accumulation in the anterolateral and apical portions of the left ventricle in the anterior view. Repeat study 3 months later demonstrated almost normal uptake but some persistence of the anterolateral defect. In Case 2 the initial scan at age 12 months demonstrated a thin ring of activity corresponding to a thin dilated left ventricle (Fig. 1). The anterolateral defect was larger than that in Case 1 and extended apically and inferiorly. Repeat study at age 14 months showed marked improvement but a persistent defect. In Patient 3, study at age 2 1/2 years showed a more extensive anterolateral and apical defect in the left anterior oblique view, indicating anterolateral and posteroinferior infarctions.

Postoperative Group

Early presentation (Patients 4 and 5): The age at presentation and clinical features of Patients 4 and 5 were similar to those of the three patients not operated on. In addition, Patient 5, who underwent preoperative catheterization, had findings similar to those of Patients 1 to 3 (Tables I and II). Intracardiac shunting was moderate, and the left coronary artery was dominant in this patient.

Elective ligation of the left coronary artery at its pulmonary arterial origin was performed in these two patients at age 4 months and 6 years, respectively. Postoperative catheterization in Patient 5 demonstrated normal pressures and oxygen saturation levels, and angiograms showed return of both coronary arteries to normal size with clear visualization of collateral vessels (Table II). Fourteen and 15 years, respectively, after operation, these patients were asymptomatic and had a normal electrocardiogram at rest. The electrocardiogram of the maximal stress test revealed 2 to 3 mm of S-T depression in the lead V_6 (Fig. 2, left). The maximal heart rate was within 15 beats/min of the predicted maximum for age, and there were no symptoms or arrhythmias.

Stress myocardial perfusion scans were normal (Fig. 2, bottom), revealing uniform uptake of thallium-201 with some thinning at the apex, which is a normal variation. The right ventricle showed slight tracer uptake.

Late presentation (Patient 6): This patient presented with a murmur at age 9 years, with only electrocardiographic evidence to suggest the diagnosis. Preoperative cardiac catheterization showed normal pressures, a moderate shunt at the pulmonary arterial level and a coronary arterial anatomy similar to that of the patients not operated on (Table I). However, left ventricular size and function were normal, and there was mild unexplained aortic insufficiency.

Electively, at age 9 years the anomalous left coronary artery arising from the pulmonary artery was ligated, and a saphenous vein graft was inserted from the aortic root to the main left coronary artery. Results of catheterization 1 to 7 years postoperatively were similar to the preoperative findings except for the absence of shunting (Table II). The graft was patent but a prolapsed right coronary cusp was seen on the second study. Seven years postoperatively the patient was well and had a normal electrocardiogram at rest and during exercise as well as a normal stress myocardial perfusion scan.

Discussion

Thallium-201 scanning, a well established means of detecting and localizing ischemia and infarction of the myocardium in adults,[10–12] has not been extensively applied to children. Neill et al.[15] demonstrated the value of thallium-201 scanning in diagnosing single ventricle, and we[16] recently showed greatly reduced thallium-201

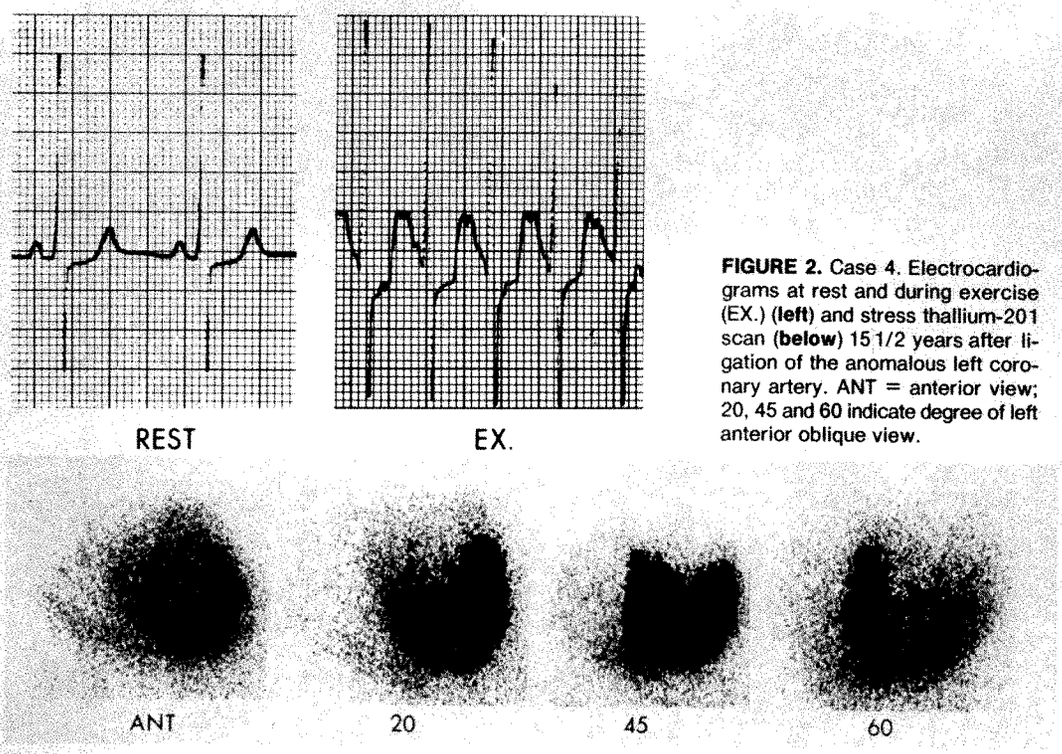


FIGURE 2. Case 4. Electrocardiograms at rest and during exercise (EX.) **(left)** and stress thallium-201 scan **(below)** 15 1/2 years after ligation of the anomalous left coronary artery. ANT = anterior view; 20, 45 and 60 indicate degree of left anterior oblique view.

uptake in the myocardium of infants with transient myocardial ischemia. One could reasonably assume that infarction would be identifiable with thallium in infants and children as it has been in adults, and recently Ferrer et al.[17] described the use of thallium-201 imaging in the diagnosis of anomalous left coronary artery. In the present study, we performed serial myocardial perfusion scans in infants with this condition, in the hope that closer follow-up of the extent of the ischemic and infarcted zones during infancy would yield more precise data on which to base prognosis and surgical intervention.

Application of thallium-201 scanning to diagnosis and determining optimal timing of surgery: To date, the only available means of monitoring the progression of myocardial infarction in infants has been the electrocardiogram or vectorcardiogram. Our study now confirms that infarction in infants is identifiable as a defect in the thallium-201 myocardial perfusion image. Repeated scans permit direct evaluation of changes in extent of ischemia or infarction and should assist in the timing of surgery (by permitting recognition of a perfusion defect that is increasing despite medical therapy). The two patients (Cases 1 and 2) who underwent repeat studies (performed within 2 to 3 months to avoid the effects on the scan of the infant's growth) demonstrated noticeable improvement in perfusion, despite an unchanged electrocardiogram. In such patients, given additional evidence of clinical improvement, we believe it is reasonable to delay surgery for at least 1 year. However, a larger perfusion defect, such as that in our Case 3, may indicate a worse prognosis regardless of the form of treatment.

Localization of perfusion defects: The localization of the zone of decreased thallium-201 uptake in our infant patients deserves comment. In all three, an anterolateral defect was seen in the perfusion image of the left ventricle, and this finding was in agreement with the localization of infarction by electrocardiogram, a technique that has been shown to be reliable.[18] In Cases 2 and 3 a posteroinferior defect evident on scanning was not indicated in the electrocardiogram. This discrepancy may have been related to the difficulty of electrocardiographic detection of posteroinferior electrical activity, particularly in children. False positive perfusion scans are unlikely,[19] although a perfusion defect can result from ischemia as well as infarction. Infants with an anomalous left coronary artery may have an ischemic zone, which would be indistinguishable from infarction on thallium-201 perfusion imaging. Technetium-99m pyrophosphate imaging may prove useful in making this distinction. Not all infarcts are detected with thallium-201 imaging. In particular, subendocardial damage is not well imaged and is frequently missed in dog studies.[11,20] The area of damaged myocardium seen in autopsy specimens of hearts with an anomalous left coronary artery is largely subendocardial[9]; thus, a subendocardial extension of the infarct may go undetected on thallium-201 imaging. In practice we suggest that in a sick infant with an anomalous left coronary artery serial thallium-201 images demonstrating extension or no change in the perfusion defect may be an indication for surgery, whereas images revealing a reduction in the defect, while possibly concealing some damage, may be an indication for continued medical therapy.

Evaluation of long-term surgical results with myocardial scans: Apart from the question of timing of surgery there is uncertainty about the long-term results of both vein bypass grafts[2,4,5,21] and ligation.[2,6,22] Thallium-201 scanning appears to be valuable for noninvasive, long-term follow-up of these procedures. Two patients who had ligation of the anomalous left coronary artery and one who had a bypass graft had normal stress myocardial scans 7 to 15 years postoperatively in association with normal clinical and cardiac catheterization findings. Why two of these three patients continued to have a positive exercise electrocardiogram is difficult to explain. The stress myocardial scan is in some ways better than the stress electrocardiogram as a test of significant ischemia in symptomatic adults with coronary artery disease.[11,12,19,23–26] Further, our three surgically treated patients were asymptomatic, and false positive stress electrocardiograms are frequent in this group.[27] However, the frequency of false negative thallium-201 scans in asymptomatic subjects is not known, and further studies of surgically treated patients with anomalous left coronary artery are needed to resolve the discrepancy between the electrocardiographic and scintigraphic findings.

The apparently normal myocardial perfusion in our three surgically treated patients is not necessarily a result of the surgical technique used or the type of operation performed. All three patients might have done well with other types of treatment and, because preoperative studies were not performed, we have no good index of the level of perfusion before surgery. One patient (Case 6) did not present until age 9, and presumably represents that group of patients with a very good collateral supply to the left ventricular wall. The two patients who underwent preoperative cardiac catheterization had a large left coronary artery. They also had the apparently favorable finding[2] of left to right shunting at the coronary arterial level (with a pulmonary to systemic flow ratio of 1.8 and of 2.1, respectively, representing a very large flow through the coronary system). The improvement in the electrocardiographic findings in all and the reduction of heart size in the two patients with cardiac enlargement preoperatively is some evidence for improvement after surgery. By contrast, electrocardiographic improvement occurred in only one of the four cases reported by Askenazi and Nadas.[2]

Correlation between coronary arteriography and myocardial scan: With the reservations indicated, some correlation might be expected between the size of the thallium-201 perfusion defect and angiographic assessment of coronary arterial anatomy and collateral vessels. Our three infants had a dilated dominant right coronary artery and proximal and distal collateral vessels between the coronary arteries. In the one infant whose left coronary artery appeared of normal size, the perfusion defect was smaller than in the two infants with a small left coronary artery. The repeat scan similarly showed more resolution of the defect in the infant with a normal-sized left coronary artery. The estimated shunt was small in all three infants. However, the difficulty of estimating defect size from images of a small heart and the small number of our patients make generalizations risky. The pathophysiologic features of a given case can be complicated by the possibility of regression of intercoronary collateral vessels in infancy, as documented in autopsy specimens,[28] wide variations in number and size of collateral vessels[28] and the influence of proximal versus distal collateral vessels (Cases 1 to 3, Table II) in determining coronary steal versus myocardial perfusion.

Clinical application: We have shown that perfusion defects can be clearly demonstrated and their evolution followed up in the infant heart with thallium-201 myocardial scanning. These techniques, possibly with the addition of other radionuclide methods (technetium-99m pyrophosphate imaging[20]), and improved resolution should provide valuable pathophysiologic information on which to base treatment of anomalous left coronary artery. Longer-term studies on both medically and surgically treated patients are necessary before the role of the perfusion study in patient management is clearly defined. With the clear demonstration of infarction with ischemia in infancy, we believe that perfusion scans can now be applied to conditions in which ischemia alone may play a role, such as severe aortic stenosis or coarctation and severe birth asphyxia.

Addendum

Since preparation of this report, Patient 2 died at age 19 months after palliative surgery. Autopsy revealed extensive endocardial and subendocardial fibrosis in all regions of the left ventricular myocardium. The ventricle was not aneurysmal, but the apical and inferior portions were greatly thinned and almost totally replaced with fibrous tissue. These findings concur with the demonstration on perfusion scan of the region of infarction, which showed extension of an inferior infarct not evident in the electrocardiogram. No areas of recent infarction were seen.

A third imaging study in Patient 1 at age 11 months demonstrated almost normal perfusion, in agreement with the excellent clinical course and improving electrocardiographic findings.

Acknowledgment

We thank Drs. J. A. G. Culham, W. G. Williams and J. E. Morch for reviewing our material and W. Bryson, chief medical photographer at the Hospital for Sick Children, for the photographic formats.

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Electrocardiographic Pseudo-Infarction Pattern: Appearance With a Large Posterior Pericardial Effusion After Cardiac Surgery

BAKR IBRAHIM SALEM, MD
MARK SCHNEE, MB, FACC
LOUIS L. LEATHERMAN, MD
CARLOS M. de CASTRO, MD, FACC*
JAIME BENREY, MD, FACC

Houston, Texas

Two patients with a large posterior pericardial effusion after cardiac surgery presented with electrocardiographic precordial Q waves without evidence of myocardial infarction. Resolution of the pericardial fluid resulted in the disappearance of the Q waves. Changes in conductivity and orientation of the heart within the pericardial space, along with a decrease in QRS voltage, could lead to the loss of initial R waves in the precordial leads, eventually resulting in a QS complex. Care should be taken in interpreting the electrocardiogram after cardiac surgery in patients with a large posterior pericardial effusion. The clinical course along with serial electrocardiographic and echocardiographic tracings should be helpful in identifying this false infarction pattern.

Electrocardiographic changes associated with pericardial disease have been described previously.[1–15] Most of these reports[1–10] stressed the sequence of ST-T changes in acute pericarditis but did not find low QRS voltage and electrical alternans in pericardial effusion. Therefore, the presence of precordial Q waves in the absence of myocardial infarction has not been discussed; on the contrary, the absence of Q waves has been considered a hallmark in differentiating acute pericarditis from myocardial infarction. In two patients we observed the temporary appearance of Q waves in the precordial leads with localized pericardial effusion after cardiac surgery without evidence of myocardial infarction.

Case Reports

Patient 1: A 58 year old man was admitted for evaluation of angina pectoris without previous myocardial infarction. Physical examination revealed a fourth heart sound. On admission the chest X-ray film and electrocardiogram were normal. Coronary arteriograms revealed 75 percent narrowing of the left anterior descending and first obtuse marginal arteries. The right coronary artery was totally occluded. The left ventriculogram was normal. Triple saphenous vein bypass grafts to the involved coronary arteries were performed with an uneventful hospital course. The postoperative electrocardiogram was unchanged.

The patient was readmitted 8 months later because of increasing dyspnea without chest pain. The physical findings included a pulse of 112/min and blood pressure of 134/100 mm Hg. The jugular venous pulse was elevated, the heart sounds were diminished with a summation gallop, and there were a few basilar rales. The chest X-ray film revealed cardiomegaly and mild pulmonary congestion. The electrocardiogram showed deep Q waves, and the echocardiogram disclosed a large posterior echo-free space due to pericardial effusion (Fig. 1). Serial determinations of serum cardiac enzymes, including creatine kinase isoenzyme, were normal. Repeat coronary angiography documented the patency of the three grafts; the patient's native coronary disease and left ventriculogram appeared unchanged. After treatment with steroids and diuretics, the pericardial effusion resolved. The electrocardiogram and the echocardiogram recorded before discharge are shown in Figure 2.

From the Division of Cardiology, the Clayton Foundation for Research Laboratory–St. Luke's Episcopal Hospital* and the Texas Heart Institute, Houston, Texas. Manuscript received February 27, 1978; revised manuscript received May 9, 1978, accepted May 10, 1978.

Address for reprints: Jaime Benrey, MD, 7000 Fannin Suite 1160, Houston, Texas 77030.

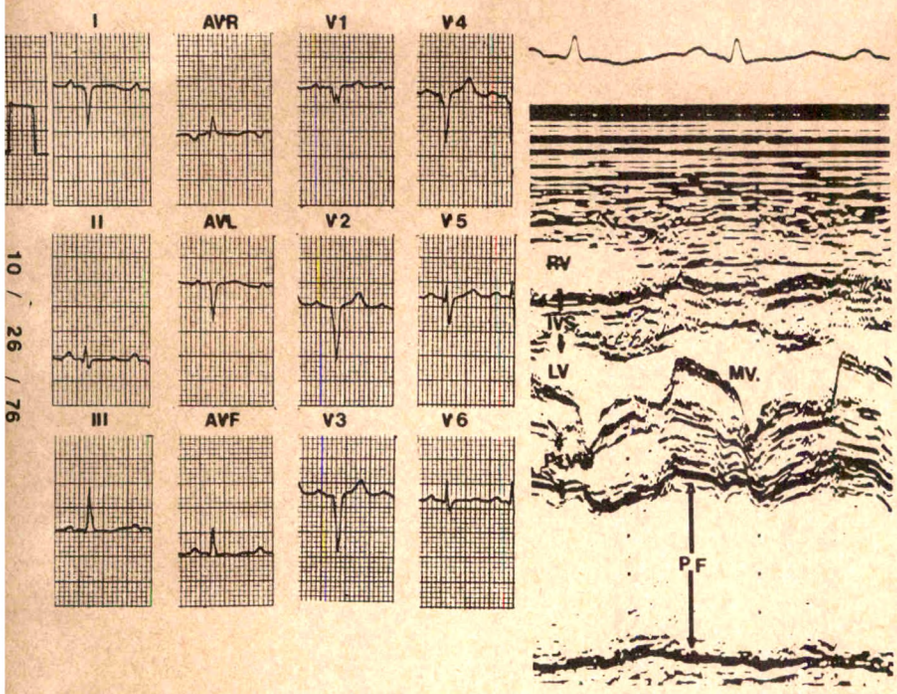


FIGURE 1. Case 1. Electrocardiogram and echocardiogram obtained when the patient presented with pericardial effusion. Note the appearance of Q waves in leads I, aVL and V_1 to V_4. The echocardiogram shows a large posterior echo-free space indicating pericardial fluid (PF). IVS = interventricular septum; LV = left ventricle; MV = mitral valve; PLVW = posterior left ventricular wall; RV = right ventricle.

Patient 2: A 35 year old man was admitted with clinically and angiographically severe aortic regurgitation. On admission the electrocardiogram disclosed left ventricular hypertrophy, and the chest X-ray film revealed cardiomegaly and pulmonary congestion. Aortic valve replacement with a no. 16 Lillehei-Kaster prosthesis was performed with an uneventful postoperative course. The electrocardiogram before discharge was unchanged.

The patient was readmitted 12 days later with sudden shortness of breath and diaphoresis. Body temperature was 38°C, pulse 125 beats/min and blood pressure 80/60 mm Hg with marked paradox. The heart sounds were distant, with no murmurs or rubs. Bibasilar rales were noted. The chest X-ray film revealed that the size of the heart had increased considerably. The electrocardiogram showed deep Q waves, and the echocardiogram revealed a large posterior echo-free space indicating pericardial effusion (Fig. 3). Cardiac enzymes in the serum were normal. A ventilation perfusion scan disclosed no pulmonary emboli. At surgery a posterior pericardial effusion was noted. After 300 cc of bloody pericardial fluid was

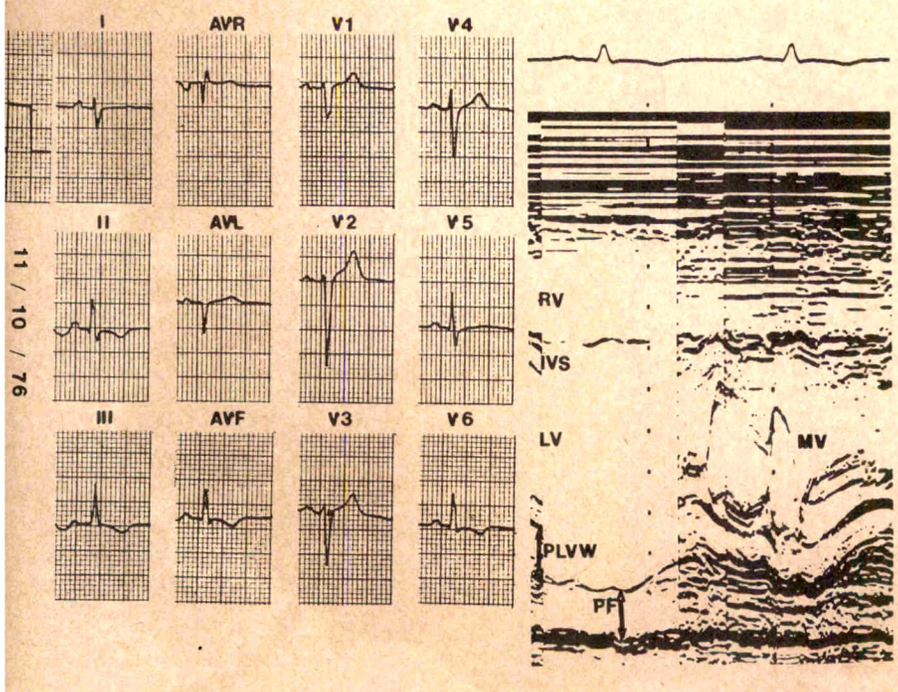


FIGURE 2. Case 1. Electrocardiogram and echocardiogram after medical treatment. Q waves are no longer present; the posterior echo-free space on the echocardiogram is significantly smaller. Abbreviations as in Figure 1.

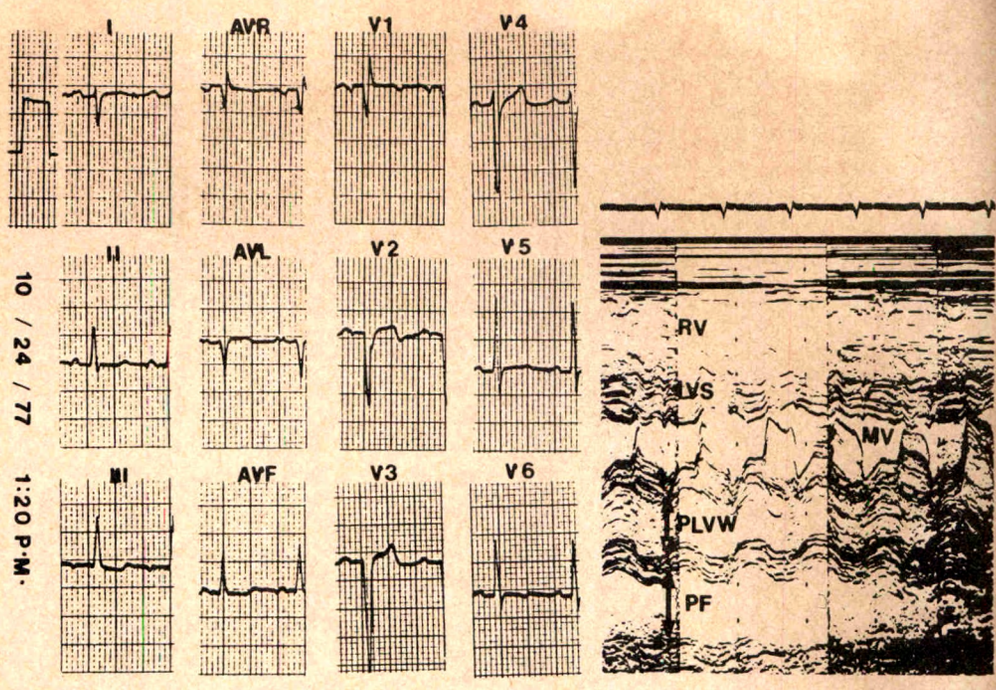


FIGURE 3. Case 2. Electrocardiogram and echocardiogram recorded when the patient presented with pericardial tamponade. Note the appearance of Q waves in leads V_1 to V_3 and the large posterior echo-free space (PF) on the echocardiogram. Abbreviations as in Figure 1.

removed, the patient's condition stabilized. A repeat electrocardiogram 6 hours later and an echocardiogram are shown in Figure 4.

Discussion

As far as we know, the presence of electrocardiographic Q waves in pericardial effusion in the absence of myocardial infarction has not been reported previously. In our patients there was no clinical or electrocardiographic evidence of myocardial infarction before or after surgery. When the first patient presented with pericardial effusion, his electrocardiogram (Fig. 1) was compatible with a diagnosis of anterolateral myocardial infarction. However, this diagnosis was considered unlikely because of the patient's history and the absence of cardiac enzyme elevation and any recognizable change in the native coronary disease and the left ventriculogram. The three aortocoronary bypass grafts were patent. With the gradual resolution of the pericardial

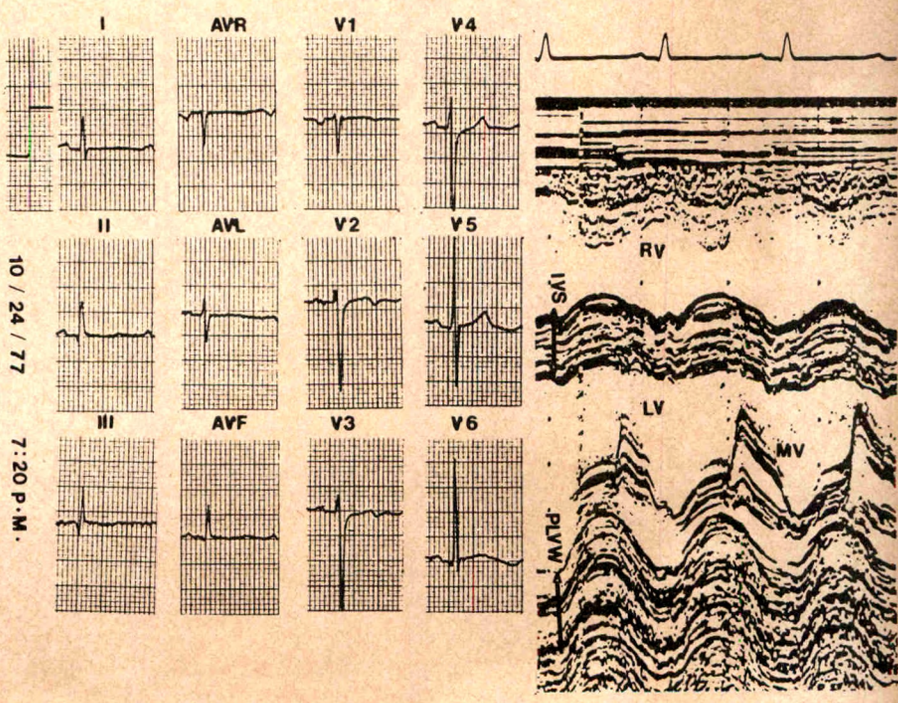


FIGURE 4. Case 2. Electrocardiogram and echocardiogram recorded on the same day, after surgical relief of the patient's pericardial tamponade. Note the disappearance of the Q waves and clearing of the pericardial fluid on the echocardiogram. Abbreviations as in Figure 1.

fluid, the R waves in the precordial leads reappeared (Fig. 2). In the second patient the electrocardiographic changes were even more impressive; the electrocardiogram (Fig. 3) simulated anteroseptal myocardial infarction, and the Q waves disappeared 6 hours after surgical relief of pericardial tamponade (Fig. 4). In both patients the QRS voltage decreased 40 to 50 percent after the development of pericardial effusion and returned toward normal when the effusion was resolved. The QRS frontal plane axis shifted to the right in both patients, and the possibility of pulmonary embolism was considered. However, the clinical course and the laboratory investigations, including a negative lung scan in the second patient, excluded this possibility.

A large localized posterior pericardial effusion was demonstrated echocardiographically in both patients and was confirmed at surgery in the second patient. There was no evidence of pneumothorax or pleural effusion in either patient to suggest cardiac displacement.

Electrocardiographic changes in pericarditis: The sequence of electrocardiographic changes in pericarditis has been described previously.[2,5,7–9] The changes include J-point and S-T segment elevation without reciprocal S-T segment depression. After the S-T segment returns to baseline value, depression of the P-R segment may occur. The T waves then progressively flatten, invert and finally become upright before regaining their original amplitude. These changes have been attributed to three factors: effusion, epicardial injury with fibrinous deposition and superficial myocarditis.[6] However, it is believed that electrocardiographic Q waves are not seen because the myocardial injury is insufficient.[6,8,10] Low QRS voltage was considered a nonspecific and inconsistent finding even in large pericardial effusions.[12,13] Electrical alternans occurs in massive pericardial effusion and may suggest tamponade.[6,8,14,15] This phenomenon has been attributed to the altered transmission of electrical potentials due to the interposition of pericardial fluid and the abnormal pendular motion of the heart within the pericardial sac.[5,6,10,12]

New Q waves after cardiac surgery: New Q waves related to cardiac surgery have been reported in 8 to 40 percent of patients, particularly after coronary bypass surgery.[21–26] Transient Q waves observed during or shortly after open heart surgery suggest that such findings are probably related to a temporary alteration in ventricular depolarization rather than to irreversible myocardial damage.[22] Myocardial infarction has been diagnosed in the majority of cases with more persistent Q waves and serum cardiac enzyme elevation. However, in such cases the presence of Q waves does not always represent transmural myocardial infarction[25]; other proposed explanations are ventricular trauma, prolonged "pump time," conduction delays[25] and unmasking of old infarctions.[26] Pericardial effusion of varying severity occurs frequently after cardiac surgery, but its association with the appearance of new Q waves has not been described. After median sternotomy, adhesions might obliterate the anterior pericardial space, leading to the accumulation of pericardial fluid posteriorly. This may cause a change in the position of the heart within the pericardial space with an apparent loss of initial septal forces. A common cause of abnormal Q waves without myocardial infarction is said to be the "abnormal or atypical position of the heart within the chest." [20] This may explain why Q waves have not been encountered in large nonsurgical pericardial effusions in the absence of myocardial infarction.

Causes of pseudo-infarction pattern: Electrocardiographic mimics of myocardial infarction have been extensively reviewed[16–20] and include ventricular hypertrophy, the preexcitation syndrome, pulmonary emboli, cardiomyopathies and technical errors. In asthenic individuals or in patients with emphysema and a low diaphragm, QS complexes occur in the anterior precordial leads because of the relatively high placement of the electrodes in relation to the heart.[20,27]

Our two cases demonstrate a pseudo-infarction pattern with a clear temporal relation to a large accumulation of pericardial fluid posteriorly. No precise explanation is given for these observations; however, changes in the electrical conductivity and the orientation of the heart within the pericardial sac in the presence of a large pericardial effusion may be responsible. Another possible explanation is that a decrease in QRS voltage may contribute to a decrease in amplitude of the initial R waves in the right precordial leads, ultimately causing a QS complex.

Acknowledgment

We thank Dr. Grady L. Hallman for permission to publish these cases, Leonard Pechacek for technical assistance and Christine Abrams for preparation of the manuscript.

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Oral Vasodilator Therapy for Chronic Heart Failure: A Plea for Caution*

MILTON PACKER, MD
JOSE MELLER, MD, FACC

New York, New York

For patients with severe congestive heart failure who continue to experience dyspnea and fatigue at rest or on minimal exertion despite optimal therapy with digitalis and diuretic agents, the supplemental use of vasodilator agents has provided a new and promising approach to therapy. Such patients generally have a greatly decreased cardiac output and an elevated left ventricular filling pressure at rest, associated with a greatly increased systemic vascular resistance and heightened venous tone. By directly relaxing venous capacitance vessels, vasodilators can reduce ventricular filling pressures and ventricular volumes; by directly relaxing arterial resistance vessels, these agents can reduce impedance to left ventricular ejection and enhance stroke volume. The enhancement of cardiac output is of primary importance because the essential feature distinguishing heart failure that is responsive or resistant to diuretic drugs is not simply the elevation of ventricular filling pressure but the adequacy of peripheral perfusion. Accordingly, whereas the use of digitalis and diuretic agents can result in satisfactory clinical improvement in most patients with congestive heart failure, such a regimen may not be satisfactory by itself in patients with low cardiac output at rest.

Sodium nitroprusside produces marked and rapid hemodynamic improvement in patients with severe heart failure.[1] However, because it can be administered only intravenously and its beneficial effects rapidly disappear when the infusion is discontinued, present work has focused on the search for an agent that is orally effective and has a prolonged duration of action. Three oral vasodilator agents have received the most attention: (1) nitrates, with effects primarily on venous capacitance vessels; (2) hydralazine, with actions predominantly on arterial resistance vessels; and (3) prazosin, with balanced effects on both vascular systems. Unfortunately, there has been widespread use of these agents without sufficient caution and without critical appraisal of the results.

Nitrates

Sublingual, oral or topical nitrates rapidly reduce pulmonary arterial pressures and ameliorate symptoms of pulmonary congestion in patients with heart failure. However, they have minimal effects on resistance vessels; thus, only a minority of treated patients[2] show significant improvement in cardiac index, relief of fatigue or restoration of diuretic responsiveness. The occasional moderate increases in cardiac index observed with nitrates may have many causes. Direct arterial vasodilation may be important in some patients, especially in those with markedly diminished cardiac output and greatly increased peripheral resistance.[3,4] Alternatively, a reduction in left ventricular end-diastolic volume may restore functional competence of the mitral subvalve apparatus and result in a diminution of mitral regurgitation with enhancement of forward output.[5] Reduction of subendocardial ischemia with improvement in regional wall motion may play an additional role in patients with ischemic heart disease. Presumably, these explanations may account for the increase in cardiac output that has also been seen with other pre-

From the Division of Cardiology, Department of Medicine, The Mount Sinai School of Medicine of The City University of New York, 1 Gustave Levy Place, New York, New York. Manuscript received June 30, 1978; revised manuscript received August 16, 1978, accepted August 16, 1978.

Address for reprints: Milton Packer, MD, Division of Cardiology, The Mount Sinai Medical Center, 1 Gustave Levy Place, New York, New York 10029.

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

load-reducing interventions, such as administration of diuretic drugs, venesection and peritoneal dialysis.[6-10]

In an individual patient, the effects of nitrates on cardiac index are unpredictable. In patients with normal or only mildly elevated ventricular filling pressures, nitrates can produce decreases in left ventricular filling pressure beyond the minimum required to maintain forward output, resulting in a sharp decrease in cardiac index, an increase in regurgitant fraction, hypotension and tachycardia.[2,11-13] Therefore, only in patients with left ventricular filling pressure exceeding 20 mm Hg can nitrates be used acutely with some measure of safety.[11] Furthermore, long-term out-of-hospital therapy with nitrate preparations has its own difficulties. Sublingual nitrates require a dosing interval of 1 to 2 hours,[14] and individual variability in absorption of oral or topical preparations makes titration of required dosages by these routes difficult without invasive hemodynamic monitoring.[2,15,16] In addition, headaches frequently prohibit continued use of these agents in the doses necessary to produce therapeutic effects.

Hydralazine

To reduce peripheral vascular resistance and increase cardiac output consistently in patients with severe heart failure, attention has turned to arterial vasodilators such as hydralazine. Marked increments in cardiac index, stroke volume and stroke work are observed with short- and long-term administration of hydralazine,[17] largely because of the decrease in peripheral resistance, although an additional direct inotropic action has been suggested.[18] Because of minimal direct effects on venous capacitance vessels, little acute reduction in ventricular filling pressure is seen except in patients with significant mitral regurgitation[19] or in those receiving large doses (100 mg).[20] With institution of maintenance therapy, a brisk diuresis occurs in many patients with subsequent rapid amelioration of dyspnea and fatigue and large reductions in diuretic requirements.

The dose requirements for hydralazine in heart failure are variable, but generally large doses are necessary: 75 to 200 mg as a single dose and 200 to 600 mg daily.[21] Several studies[17,21,22] have indicated that the administration of less than 200 mg daily is unlikely to be associated with significant hemodynamic and clinical benefit. The large doses are unexpectedly better tolerated by patients with severe heart failure than by hypertensive patients without heart failure, because significant tachycardia or hypotension is generally not observed with vasodilator therapy in patients with low cardiac output and high ventricular filling pressures. Indeed, as cardiac performance improves and peripheral perfusion is restored, heightened sympathetic tone is reduced and heart rate may decrease.[23] Likewise, significant hypotension occurs only when ventricular filling pressure is reduced excessively or the decrease in peripheral resistance surpasses the ability of the induced increase in cardiac output to support arterial pressure. Because these events are unlikely to occur with hydralazine, the agent may provide substantial hemodynamic benefit with few circulatory risks. Although hemodynamic variables show improvement within hours of drug administration, amelioration of dyspnea and fatigue may be less rapid; in our experience, clinical responses have been delayed up to 1 week after the initiation of maintenance hydralazine therapy, because they seem dependent in part on the occurrence of a drug-induced diuresis.

The major drawbacks to hydralazine therapy are dose-related adverse effects. Headaches are frequent (occurring in one third of patients), although they subside in most patients despite continued therapy. Idiosyncratic reactions (fever, rash, thrombocytopenia) are occasionally seen. Myocardial ischemic events may occur in patients with underlying coronary artery disease despite the absence of associated tachycardia.[24] Although the possibility of producing a lupus-like syndrome with long-term administration of large doses of hydralazine has provoked concern, we believe that this is a risk worth taking, considering the potential benefits to be derived from this agent in critically ill patients.[25]

Prazosin

Much interest has recently been generated in the use of a new orally effective alpha sympathetic blocking agent, prazosin, for balanced preload and afterload reduction in patients with severe heart failure. A marked reduction in ventricular filling pressure and a significant increase in cardiac index are observed with first doses of the drug.[26] However, despite earlier reports of sustained clinical improvement with long-term administration,[27] prolonged hemodynamic monitoring for 72 to 96 hours has documented the rapid development of clinical and hemodynamic tachyphylaxis after 2 to 3 days of maintenance therapy.[28] Even rapid increments in dosage, up to 30 to 45 mg daily, are not accompanied by sustained benefit in the majority of patients. In our experience, only about 30 percent of patients have persistent effects from this agent with chronic use. These observations seem to be the hemodynamic counterpart of the "first dose phenomenon" described in antihypertensive therapy,[29] in which exaggerated responses are observed with the initial administration of prazosin, but minimal effects are observed in most patients with continued use of the same or even larger doses.

The eventual role of prazosin in heart failure is unclear at this time. Invasive hemodynamic monitoring is necessary to identify those patients who demonstrate persistent beneficial effects with repeated drug administration. In the majority of patients, the drug is unlikely to play a major role in long-term therapeutic preload and afterload reduction. In these patients, prazosin may in the future best be utilized for acute heart failure not rapidly responsive to conventional methods, when the administration of nitroprusside is not feasible. We have used it as intermittent therapy in patients with heart failure during exacerbations of symptoms or to initiate a diuresis in patients who may still be managed with diuretic agents alone.

General Application

Because patients with refractory heart failure manifest both low cardiac output and high ventricular filling pressure, emphasis has been placed on the need for balanced preload and afterload reduction with vasodilator drugs, such as is seen with prazosin, nitroprusside or hydralazine-nitrate combinations. Because the essential feature of diuretic-resistant heart failure is greatly decreased cardiac output and stroke work, the administration of a predominantly arterial vasodilator (hydralazine) alone to increase stroke work should restore responsiveness to conventional diuretic agents; once peripheral perfusion improves, adequate reduction in left ventricular filling pressure can then be achieved with furosemide or ethacrynic acid. Consequently, after maintenance therapy with hydralazine is established, the need for chronic preload reduction with supplemental nitrates is not clear. This would only seem necessary in patients with underlying ischemic heart disease or diuretic resistance due to advanced renal insufficiency. Supplemental nitrates are also useful in the rapid relief of dyspnea in patients with greatly elevated left ventricular filling pressure. However, once hydralazine has improved cardiac performance and restored diuretic responsiveness, the requirement for continued administration of nitrates should be reevaluated.

Should vasodilator therapy be used in patients with heart failure still responsive to conventional management? In our experience refractory heart failure has generally corresponded to a cardiac index of less than 2.5 liters/min per m^2, a stroke work index of less than 20 to 25 g-m/m^2 and a left ventricular filling pressure greater than 15 mm Hg at rest. This characteristic baseline hemodynamic profile is important because responses to vasodilator agents vary according to the baseline hemodynamic state. Potentially detrimental hemodynamic consequences may accompany the use of vasodilators in patients with a cardiac index of more than 2.5 liters/min per m^2 or a left ventricular filling pressure of less than 15 mm Hg, or both, because of an increase in regurgitant volume, a reduction in cardiac output and severe hypotension.[2,11–13,30] Although such patients may demonstrate hemodynamic deterioration and become severely symptomatic upon modest exertion, there is little evidence that exercise performance is improved in these patients with vasodilators, possibly because exercise provokes vasodilatation overlapping the vasodilatation that can be achieved pharmacologically.[31,32] As a result, the role of vasodilators in patients with milder degrees of heart failure and normal hemodynamic variables at rest is open to question. We now reserve the use of these agents for patients with dyspnea and fatigue on minimal exertion refractory to conventional therapy with digitalis and diuretic drugs; invasive hemodynamic characterization is then performed, and the administration of vasodilators is undertaken only when an appropriate hemodynamic profile is present.

The underlying etiology and pathophysiology of heart failure are important determinants of the response to impedance reduction. Patients with advanced left ventricular dysfunction associated with greatly increased ventricular end-diastolic volume respond well, regardless of the underlying etiology, but those with underlying ischemic heart disease may be at special risk.[24] Patients with severe mitral or aortic regurgitation may experience additional improvement from the reduction in regurgitant volume when peripheral resistance decreases, but the regurgitant fraction may increase if preload reduction is excessive.[12] The administration of vasodilator agents may be distinctly detrimental when heart failure is due to valve obstruction or associated with a nondilated hypertrophic cardiomyopathy; these states require a high level of filling pressure to maintain adequate cardiac output. Furthermore, the usefulness of these drugs in patients with heart failure associated with cor pulmonale, tricuspid regurgitation or infiltrative myocardial disorders is unclear.

Future Prospects

Newer vasodilator agents that can be more easily titrated and better tolerated than those now available need to be developed; orally effective angiotensin blocking agents or vascular smooth muscle-specific prostaglandins may be promising approaches.[33,34] Radionuclear or echocardiographic techniques could be sufficiently refined to permit noninvasive determination of hemodynamic abnormalities and facilitate evaluation of drug-mediated improvement. Controlled studies will become necessary to determine whether long-term vasodilator therapy alters the natural history of patients with heart failure, whether they are asymptomatic patients with established hemodynamic abnormalities or severely disabled patients still responsive to conventional medical therapy.

At present, vasodilator drugs have a definite role in the management of patients with refractory heart failure. However, they should not be used indiscriminately, and invasive hemodynamic monitoring should be used to guide their administration. Such monitoring permits determination of an appropriate baseline hemodynamic profile, allows for individualization of effective drugs and dosage requirements and makes possible substantiation of sustained hemodynamic improvement. In this way one can avoid the use of empirically determined therapy that may commit patients to long-term ineffective treatment with potentially dangerous drugs.

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LETTERS TO THE EDITOR

ECHOCARDIOGRAPHY AND PROSTHETIC VALVE MALFUNCTION

Bernal-Ramirez and Phillips[1] correctly state that echocardiography can be helpful in identifying valve malfunction. However, we do not agree with some of their statements and interpretations of their data.

Their report is not the first on echocardiographic findings in malfunctioning Bjork-Shiley mitral valves; at least two publications appeared earlier.[2,3] The "hump," that is, protodiastolic anterior motion, with perivalve leak, occurs not only in patients with a Bjork-Shiley valve but also in patients with Starr-Edwards and Beall valves, and it disappears after surgical repair.[2] We have made the same observation in a patient with a dehiscent Cooley-Cutter valve. Yuste et al.[2] pointed out that protodiastolic anterior motion represented motion of the whole prosthesis. In our patient we found (using echocardiography and cinefluoroscopy) that the valve opening was completed at the onset of protodiastolic anterior motion. We have also seen the latter motion with transvalve regurgitation (in the absence of dehiscence and perivalve leak). Close inspection of Figure 3 of Bernal-Ramirez and Phillips suggests that this could be another example of protodiastolic anterior motion with transvalve regurgitation. The speculation on the cause of protodiastolic anterior motion is not clarified. Increased rapid diastolic filling of the ventricle would be more likely to result in posterior motion of the valve. Abnormal prosthetic mobility or disc oscillations could have been ascertained with fluoroscopy in appropriate angulation.

Delayed opening and closing of a prosthetic valve, as one feature of malfunction secondary to thrombus formation, has previously been documented with echocardiography and phonocardiography.[4] However, delay of opening or closure is not evident in the tracings shown by Bernal-Ramirez and Phillips. In addition, they give no data on how they determined the normal point of opening without simultaneous phoncardiography in the presence of a flat ST-T segment, especially in a patient with irregular R-R intervals (their Case 1). What they interpret as slow motion of the disc could as well represent motion of the whole prosthesis comparable with the pattern seen in a severely stiffened immobile mitral valve. In dehiscent prosthetic valves, excursion of the whole prosthesis can be increased.[5] Furthermore, in the presence of multiple echoes, measurement of the opening and closing slope may result in large errors, especially at paper speeds of 50 mm/sec.

Ulrich W. Busch, MD
Virendra S. Mathur, MD, FACC
Efrain Garcia, MD, FACC
Robert J. Hall, MD, FACC
Clayton Foundation for Research—
St. Luke's Episcopal Hospital
Texas Heart Institute
Houston, Texas

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REPLY

We do not find it very important whether our article was "first" or not. What is important is that information dealing with the echocardiographic diagnosis of Bjork-Shiley prosthetic valve malfunction had not previously reached a wide audience. Our publication provided for that. It should be noted that our observations were independent ones made without knowledge of the references noted by Busch et al. A thorough computer library search for the topic in question did not produce those references. Further, those reports dealt with only one form of valve malfunction.

We welcome the opinions noted in the remainder of the letter. Although we are not in consistent agreement with these opinions we believe that further polemic would not be productive. Additional experience since the publication of our paper has reinforced our earlier findings. We remain confident that the information we provided will continue to be of sound value in the echocardiographic diagnosis of Bjork-Shiley prosthetic mitral valve malfunction.

Jose Alberto Bernal-Ramirez, MD
John H. Phillips, MD, FACC
Department of Medicine
Cardiology Section
Tulane Medical Center
New Orleans, Louisiana

LEFT VENTRICULAR PRESSURE IN AORTIC STENOSIS

Aziz and his associates[1] have provided a valuable approach to the patient with aortic stenosis. However, one formula in their study may be misunderstood or misused. The authors suggest that in patients with aortic stenosis and without myocardial decompensation, the left ventricular pressure (mm Hg) may be given by the formula "$6 + 298\ (\bar{h}/r) \pm 13.4$." Although the last term in this expression is the standard deviation about the regression, or the standard deviation of the differences between actual and predicted left ventricular pressures, this term does not represent limits around an individual prediction. These limits may be calculated,[2] and they are wider than the standard deviation. In this case, the 95 percent confidence interval is ±28 mm Hg at its narrowest point, which coincides with the mean left ventricular pressure in the sample (about 150 mm Hg). Although the results of the study are quite significant, further experience is necessary before one can reliably use this formula to predict left ventricular pressure accurately.

Thomas Riggs, MD
Stephen Hirschfeld, MD
Rainbow Babies & Children's Hospital
Cleveland, Ohio

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REPLY

Riggs and Hirschfeld are quite correct in their interpretation of the last term in our formula as the standard deviation about

the regression. The relation is highly significant and shows potential as a predictive tool, but we agree that further experience is necessary.

The standard deviation of error from the regression estimate is a valid and generally understood statistic. If we had been proposing this relation as a specific predictive tool then we would have defined several different confidence levels. The variation due to errors in estimating the regression parameters also would have been included. In our study, the 95 percent confidence limits would be ±29.0 mm Hg at the narrowest point, not the 28 mm Hg stated by Riggs and Hirschfeld. At the upper extreme range of the observations, 95 percent confidence limits of ±32.4 mm Hg reflect errors in the estimate of the parameter b = 298. This means that for an $\bar{h}/r$ ratio of 0.71 the estimate is 217.9 ± 32.4 mm Hg, or 95 percent confidence limits of 185.4 to 250.3. In spite of the amount of variation, we believe that such estimates are good enough to be very useful, although further refinements and additional observations may improve our estimate of the best predictive tool.

Kalim U. Aziz, MD
Milton H. Paul, MD, FACC
Albertus van Grondelle, MS
Alexander J. Muster, MD, FACC
Division of Cardiology
Willis J. Potts Children's Heart Center
The Children's Memorial Hospital
Chicago, Illinois

PORCINE HETEROGRAFTS IN TRICUSPID POSITION

In their report on structural change in porcine heterografts, Spray and Roberts[1] described five stenotic and thrombosed bioprosthetic valves. Although tricuspid valve replacement accounted for 29 percent of replaced valves, thrombotic stenosis of bioprostheses in the tricuspid position accounted for 40 percent of all thrombosed and stenotic valves. Fishbein et al.[2] reported on one patient in their series who underwent tricuspid valve replacement and who died 5 days postoperatively in a low output state. No anatomic cause was found to explain this patient's death. This relatively large incidence of thrombotic and low output complications associated with the stent mounted porcine heterograft in the tricuspid position should not be surprising because the valve is, most likely, structurally unsuitable for the low pressure right-sided atrioventricular position. While evaluating the echocardiographic appearance of this valve,[3] we found that the valve leaflets did not open fully when exposed to lower levels of flow. With decreasing flow past the valve, there was decreasing leaflet movement. At a very low stroke volume, the posterior muscular leaflet did not move at all.

Thrombosis about the tricuspid position bioprosthesis may have been induced by stasis of blood around the valve caused by incomplete valve opening and a low cardiac output. The porcine aortic tissue evolved over a million years to be opened rapidly by a high pressure ventricle. A grossly dilated and fibrillating right atrium, which is present in most patients with advanced tricuspid valve disease, may not generate a sufficient rate of rise of pressure to open this bioprosthesis adequately.

Michael S. Horowitz, MD, FACC
Division of Cardiology
The Mountainside Hospital
Montclair, New Jersey

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REPLY

Horowitz may indeed be right in his contention that there is a relatively large incidence of thrombotic complications associated with stent mounted porcine heterografts in the tricuspid position and that these substitute cardiac valves may not be suitable for the low pressure of the the right-sided atrioventricular valve position. He may indeed be right, but I think there is not enough information to make that judgment at the moment. We simply reported the observations made in the necropsy patients we have studied. From our study it would not be possible to come to a conclusion regarding increased frequency of thrombus formation on the right-sided valve compared with the left-sided valve and certainly not the conclusion that this prosthesis is unsuitable for the tricuspid valve position.

William C. Roberts, MD, FACC
Pathology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

SUDDEN DEATH: HOW UNEXPECTED?

The case reported by Lawrence E. Hinkle et al.[1] was heralded as an example of "unexpected sudden death," yet throughout the report there is evidence of increasing hypertension, documented rhythm disturbances, anginal episodes (up to 10 daily) and, finally, symptoms compatible with early left ventricular failure. Certainly these symptoms and findings would lead the astute clinician to conclude that sudden death was a real probability.

Second, the report makes no mention of the patient's ever receiving adequate treatment for his hypertension, rhythm disturbances or angina pectoris. In fact, the only medication the patient was receiving was Coumadin,® 2.5 mg/day. Furthermore, there is no evidence that the patient had a thorough cardiac evaluation with echoelectrocardiography, and particularly coronary arteriography, to delineate whether he might have been helped with surgical myocardial revascularization. It is conceivable that these aspects of the patient's course were deleted from the case report; if not, the lack of diagnostic and therapeutic medical attention in this 61 year old man seems appalling.

John E. Mielke, MD
Appleton, Wisconsin

Reference

1. **Hinkle LE Jr, Argyros DC, Hayes JC, et al:** Pathogenesis of an unexpected sudden death: role of early cycle ventricular premature contractions. Am J Cardiol 39:873–879, 1977

REPLY

The subject of our report was invited to participate in our studies because his medical record at his employer's indicated that he was probably at high risk of sudden death. He and 332

similar men, employed in 19 industries, two labor unions and two public authorities in the New York metropolitan area, volunteered to take part in these studies. It was agreed that these men would continue under the care of their private physicians and that we would forward complete reports of our findings to their private physicians and (with their written permission) to their company physicians as well.

When this man was first examined in 1971, a letter describing in detail all of our findings and all our recommendations was sent to his physicians, and our examining physician discussed these with the participant himself in detail. At subsequent examinations, when there were significant new findings, these were also discussed with him and were communicated to his physicians.

The patient's role: The chief obstacle to the adequate treatment of this man was his own personality. He minimized his symptoms, sometimes denied their existence and concealed them from his associates. He disdained medication, preferred not to take nitroglycerin for his angina and would not change his routine of activities in any way. In 1973, in the interval between examinations, electrocardiographic evidence of a new myocardial infarction developed, but he denied having had any symptoms during this period and he lost no time from work. On many occasions he would not visit his physician regularly despite his physician's urging and our urging. At the time of his death he had not seen his physician for 3 months. The story of his increasing shortness of breath and probable congestive heart failure occurring in the weeks before he died was obtained more from his wife and friends than from him, and most of the information was obtained after his death.

Role of clinical findings: Other features of his case, in addition to his concealment of symptoms, tended to obscure the seriousness of his condition. His hypertension was manifested mostly during the day when he was active and challenged by his surroundings. When he was in his physician's office or at the company medical department his blood pressure was repeatedly recorded in the range of 130/80 mm Hg. The shadow of his heart on X-ray examination did not reflect the magnitude of his myocardial hypertrophy. The cardiothoracic ratio remained less than 50 percent. It was not until late in his course that roentgenologists began to describe his heart as "enlarged." The evidence of an electrocardiographic "pattern of left ventricular hypertrophy" was limited to an R wave of 15 mm in lead aVL. Echocardiography, which might have revealed the hypertrophy, was not available as a part of the original protocol in 1971. Thus, with the information available during much of his course, there was legitimate medical reason to question whether he required antihypertensive treatment.

To the casual medical observer, to whom this man minimized his symptoms, he appeared to be an active person with labile hypertension who had had two myocardial infarctions in the past but who was doing relatively well. As for his arrhythmias, his ventricular premature complexes were few (less than 1/1,000 complexes), asymptomatic and discernible only on tape recordings. The importance of early cycle ventricular premature complexes in the pathogenesis of sudden cardiac death outside the hospital was not appreciated until several years after his initial examination.

Prevention of sudden death: Regardless of these considerations, Mielke raises an important question with regard to unexpected sudden cardiac death. Our studies and the reports from Seattle and Miami all indicate that sudden cardiac death occurs only rarely in people without previously detectable heart disease. In the majority of cases it occurs in people with readily recognizable heart disease whose seriousness is not appreciated. Our experience also suggests to us that failure to control the hypertension, the congestive heart failure, the evidence of ischemia, the patterns of activity and probably the body weight and metabolic abnormalities of the patient may cause "unexpected sudden death" to occur sooner than it otherwise might. Thus it appears to us that although the primary control of "risk factors" for heart disease may lie within the realm of preventive medicine and public health, the immediate prevention or delay of sudden cardiac death must be the primary responsibility of physicians who are engaged in the long-term care of patients with heart disease.

Lawrence E. Hinkle, Jr., MD
The New York Hospital-
Cornell Medical Center
New York, New York

SEPTAL DEFECT IN TRANSPOSITION OF GREAT ARTERIES

Hazan et al.[1] state that their patient survived to age 9 years "in spite of the coexistence of a complete form of atrioventricular (A-V) canal." Although no one can deny the importance of the serious hemodynamic disturbances caused by A-V canal, it was precisely the presence of this large A-V defect that permitted their patient's survival and caused her to have only "slight cyanosis." Had there been no septal defects, the severity of the malformation would have been due to the fact that—in the authors' own words—"blood circulation is the same as in transposition of the great arteries," that is, a severe, poorly tolerated and deeply cyanotic condition. One must bear in mind that the artificial creation of a large atrial septal defect (atrial septostomy) salvages many infants with transposition of the great arteries, again precisely because it allows a bidirectional shunt across the newly created defect and it improves arterial oxygen saturation. The authors' patient already had a very large septal defect permitting a large and useful bidirectional shunt.

Hazan et al. discarded the term "isolated ventricular inversion in situs inversus" because ". . . in total situs inversus, ventricles are inverted by definition." Not so. In situs inversus all the heart chambers and all the viscerae are the mirror-image of normal and therefore *the ventricles are not inverted for this situs*. Yet, a given case of situs inversus, such as the authors' (and ours mentioned in their Reference 4), *may have inverted ventricles for the situs*, but not "by definition." For this reason we have proposed a logical sequence of analytical steps in such complex specimens: (1) diagnosis of the situs; (2) diagnosis of the direction of the apex; (3) diagnosis of the truncoconal morphology (crossed arteries, transposed arteries or single trunk); (4) diagnosis of the position of the ventricles; and (5) diagnosis of the associated defects.[2,3]

J. Espino-Vela, MD, FACC
Mexico City, Mexico

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2. **Espino-Vela J:** Malpositions of the heart. G Ital Cardiol 5:811–815, 1975
3. **Anselmi G, Munoz S, Blanco P, et al:** Systematization and clinical study of dextroversion, mirror-image dextrocardia and laevoversion. Br Heart J 34:1085–1098, 1972

REPLY

We are fully aware that an atrial septal defect permits survival in transposition of the great arteries, as well as in isolated ventricular inversion. We meant to point out that this patient survived to age 9 years in spite of the presence of a complete

atrioventricular canal, which is a rather severe lesion in comparison with an ostium secundum type of atrial septal defect.

Whether ventricles are *inverted* in situs *inversus* can be disputed. We preferred to avoid ambiguity by using the term ventricular discordance, which is accurate whatever the situs may be. This discussion indicates the need for an international nomenclature for these complex anomalies.

Eric Hazan, MD
Hôpital Laënnec
Paris, France

DIASTOLIC AND SYSTOLIC SEPTAL MOTION IN PATIENTS WITH MITRAL STENOSIS

Weyman and associates[1] described the patterns of diastolic interventricular septal motion seen with M mode and cross-sectional echocardiography in patients with mitral stenosis. They noted that the magnitude of the initial diastolic dip in interventricular septal motion, which served as the criterion for separating their patients into groups IIA and IIB, may vary within a record depending on the sector selected for analysis. However, the magnitude of this diastolic dip also varies with the duration of the preceding cardiac cycle.

Because left ventricular filling depends on the size of the mitral valve orifice, the pressure gradient across this valve and the duration of diastole, and because the relative position of the interventricular septum is affected by left ventricular filling, we are currently studying relative interventricular septal position and *systolic* motion as functions of mitral valve orifice size and the diastolic interval of the preceding cardiac cycle in patients with mitral stenosis and atrial fibrillation. In Figure 1, an echocardiogram from a patient with mitral stenosis and a variable diastolic interval, left ventricular filling is so compromised relative to right ventricular filling as to shift the interventricular septum to a relatively posterior position during short cycles. During systole, after an abbreviated cardiac cycle, as in the two cycles after the second vertical arrow in Figure 1, this phenomenon may attentuate the magnitude of the diastolic dip and augment apparent paradoxic systolic septal motion. After longer diastolic intervals, left ventricular filling across the stenotic mitral valve orifice may be more complete, the interventricular septum moving to a relatively anterior position and, with systole, "squeezing" posteriorly (curved arrows). Then the subsequent diastolic dip is augmented. This cycle to cycle variation in relative interventricular septal systolic and diastolic motion can also be seen in Figure 2, A and B, of Weyman et al.

Estimation of mitral valve orifice size in patients with mitral stenosis who also have atrial fibrillation is challenging, even with cardiac catheterization. By combining the analysis of the multiple echocardiographic variables described with an analysis of diastolic interventricular septal motion as elucidated by Weyman et al., and in addition relating both diastolic and systolic interventricular septal motion to the duration of diastole in the preceding cycle, it may be possible to obtain more accurate objective evaluation of patients with mitral stenosis.

John E. Douglas, MD, FACC
Little Rock, Arkansas

Reference

1. **Weyman AE, Heger JJ, Kronik C, et al:** Mechanism of paradoxical early diastolic septal motion in patients with mitral stenosis: a cross-sectional echocardiographic study. Am J Cardiol 40:691–699, 1977

REPLY

We have likewise noted that the magnitude of the diastolic septal dip observed in patients with mitral stenosis is affected by preceding cycle length. It is attractive to conclude that the increase in diastolic cycle length results in more complete emptying of the ventricle during the following systolic contraction. This more complete emptying might then exaggerate the disparity in the rate of filling of the two ventricles during the next diastole, resulting in a more pronounced shift in initial diastolic septal position. However, the end-systolic dimension does not appear to change markedly from cycle to cycle, thus suggesting that although the end-diastolic volume and ejection fraction may vary depending upon preceding cycle length, the ventricular volume at the onset of ventricular filling may not change greatly. This is an intriguing area and we await with interest the results of Douglas's investigation.

It was not our intention to suggest that it was feasible to use diastolic septal motion as a means of estimating mitral valve orifice size. As indicated in our paper, a number of factors other than mitral valve orifice size affect the relative rate of filling of the two ventricles (for example, tricuspid stenosis

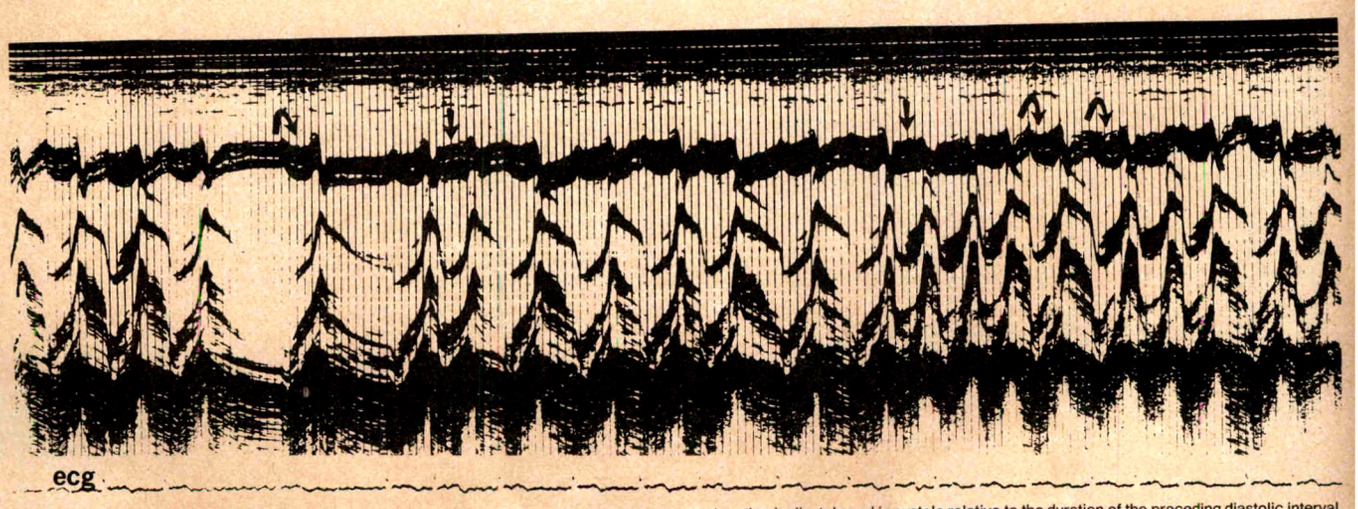


FIGURE 1. Echocardiogram of patient with mitral stenosis. Note the variation of interventricular septal motion in diastole and in systole relative to the duration of the preceding diastolic interval. ecg = electrocardiogram.

and mitral and aortic insufficiency), thus limiting the value of septal motion as a means of estimating orifice size. In addition the more recent advances in cross-sectional echocardiography have shown that the mitral valve orifice can be directly visualized and measured in the vast majority of patients, thereby making it unnecessary to obtain inferential estimates of mitral valve orifice size based on nonspecific secondary changes in cardiac motion.

Arthur E. Weyman, MD, FACC
Indiana University School of Medicine
Indianapolis, Indiana

COMPLICATIONS AFTER PROVOCATION OF CORONARY SPASM WITH ERGONOVINE MALEATE

Several reports have documented the utility of pharmacologic provocation of coronary arterial spasm using ergonovine maleate.[1–4] The relative safety of this intervention and the very prompt reversal of chest pain and electrocardiographic changes after sublingual administration of nitroglycerin have been emphasized.[1,4,5] However, Nelson and associates[6] described frequent premature ventricular depolarizations in one patient and second degree atrioventricular (A-V) block in another after administration of ergonovine, and Curry et al.[3] reported complications (supraventricular tachycardia, premature ventricular depolarizations and one instance of third degree A-V block) in 11 of 60 patients given the drug. MacAlpin[7] recently summarized the benefits and potential hazards of provocative testing for coronary spasm. The following case is germane to this topic.

Report of case: A 56 year old man was admitted to the Salt Lake Veterans Administration Hospital for coronary angiography in April 1977. In April 1975 an inferior wall myocardial infarction had been documented with serial electrocardiograms and serum enzyme data. One month later he was readmitted to the hospital because of recurring substernal chest pain. While undergoing evaluation in the coronary care unit he had several episodes of pain that lasted from 5 to 60 minutes and required one to several sublingual nitroglycerin tablets before subsiding. During episodes of pain an electrocardiographic monitor lead showed transient S-T segment elevation of up to 10 mm in magnitude. There was no laboratory evidence of myocardial necrosis. Selective coronary arteriograms obtained on April 18, 1975 were interpreted to show diffuse wall irregularity with areas of minimal luminal narrowing in the proximal portion of all three major vessels; no lesions judged to be hemodynamically significant were found. A presumptive diagnosis of coronary arterial spasm was made. The patient was treated with oral isosorbide dinitrate but was unable to tolerate doses of more than 10 mg every 4 hours because of severe symptomatic orthostatic hypotension. He continued to have chest discomfort typical of myocardial ischemia, sometimes precipitated by exertion but more often occurring at rest and characteristically awakening him from sleep at 5:00 AM. The pain lasted from a few minutes to 2 hours and often required numerous nitroglycerin tablets before subsiding completely.

Administration of ergonovine: Because of increasing frequency of chest pain he underwent repeat angiographic studies on April 5, 1977 to assess whether significant progression in the fixed coronary lesions had occurred and to elucidate the pathophysiology of his pain. Selective coronary arteriograms before the administration of ergonovine again revealed diffuse wall irregularity, with areas of fixed, mild (less than 30 percent luminal narrowing) obstruction in the proximal portions of all three major vessels. Ergonovine maleate was then administered into the distal ascending aorta. Three bolus injections of 0.05 mg each were given over a 19 minute period. This did not result in chest pain or S-T segment changes in the monitoring electrocardiogram. A bolus dose of 0.20 mg was then given. Four minutes later the patient complained of severe anterior chest pain and S-T segment elevation of 5 mm was noted on the monitoring lead II electrocardiogram. The chest pain was initially associated with frequent premature ventricular complexes, followed shortly thereafter by numerous brief bursts of ventricular tachycardia. Lidocaine was administered intravenously, but ventricular arrhythmias persisted until a total of three 100 mg bolus doses had been given over a 10 minute period. Nitroglycerin (0.4 mg) was administered sublingually at 4 minute intervals simultaneously with antiarrhythmic therapy. Chest pain and S-T segment elevation persisted for 14 minutes, finally subsiding after the third dose of nitroglycerin. However, the latter dose was also followed by systemic hypotension, aortic pressure decreasing from 100/70 to 78/54 mm Hg. The hypotension responded to leg elevation and the rapid infusion of 300 ml of normal saline solution. Selective right coronary arteriography during pain demonstrated severe spasm, with complete occlusion of the vessel in its mid portion and greatly delayed clearing of contrast material. A repeat right coronary injection after the disappearance of pain and S-T segment elevation showed nearly complete resolution of the coronary spasm.

Implications: Our patient clearly illustrates that provocative testing for coronary artery spasm may be associated with significant untoward effects that are not always easily reversed after administration of nitrates. It is conceivable that the unusual duration and resistance to nitrates of ergonovine-induced coronary spasm in this case was in part related to intraaortic administration of the drug with the possibility of partial intracoronary injection. This seems unlikely because the injection was made into the distal portion of the ascending aorta, with only slight manual pressure being applied to the injecting syringe. Because administration of ergonovine frequently produces complete or near-complete occlusion of major coronary vessels,[2–5] it might be anticipated that this would occasionally result in life-threatening complications such as major disturbances of cardiac rhythm and conduction or acute left ventricular decompensation. As this intervention becomes more widely employed it would not be surprising if rare instances of irreversible complications, such as myocardial infarction and death, were to occur. These considerations emphasize the need for extreme caution and careful patient selection in the performance of provocative tests for coronary spasm.

Dennis Bauman, MD
Department of Medicine
University of Utah College of Medicine
and
The Salt Lake Veterans Administration Hospital
Salt Lake City, Utah

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COMMENT: I

We have a great deal to learn about coronary spasm. At this time, the prevalence of spasm in patients with chest pain with or without anatomic coronary lesions is unknown. Aside from scattered case reports, the lethality of spasm as well as its role in converting coronary disease with stable angina pectoris into acute myocardial infarction is also unknown. That provocative testing for spasm carries risk is certain. The question of whether the risk is worthwhile will ultimately be answered in a general way by the collection of more information about the natural history of coronary spasm. In an individual case, a decision to attempt to provoke a potentially life-threatening entity will (and should) always be a difficult one, made with the patient's full understanding and agreement and carried out with appropriate caution.

Catherine Nelson, MD
Stanley A. Forwand, MD, FACC
Harvard Medical School
Mount Auburn Hospital
Cambridge, Massachusetts

COMMENT: II

Dr. Bauman reports on a man with probable Prinzmetal's angina and relatively normal coronary arteries who experienced severe unrelenting chest pain and arrhythmias due to near-occlusive right coronary arterial spasm in response to provocative administration of ergonovine maleate. This case emphasizes the need for a careful and systematic approach to such induction of coronary spasm in patients with suspected Prinzmetal's angina. The points to be learned from this case are as follows:

1. Reproduction of the coronary spasm and clinical syndrome of Prinzmetal's angina by ergonovine maleate is certain to be accompanied occasionally by arrhythmias because of their large incidence during spontaneous episodes.[1,2]

2. The route of administration of ergonovine maleate may be important. Reported series have utilized only intravenous administration, allowing substantial dilution before coronary arterial perfusion.[3–5] The intraaortic or intracoronary route should be reserved for investigational purposes.

3. Methodic sequential administration of increasing doses of ergonovine maleate may be important. Reports of series have generally utilized doses of 0.1 to 0.4 mg. Because patients with Prinzmetal's angina appear to be sensitive to a certain dose of ergonovine maleate, we urge a sequential increase in dosage based on reported experience, that is, 0.1 mg initially, 0.15 mg at 3 and 0.2 mg at 3 to 5 minute intervals with serial angiograms to document effect. If the patient has had documented spontaneous episodes of S-T elevation 0.05 mg should be given as the initial dose.

4. Repeat coronary arteriography, at least of the suspect coronary artery, should be performed after each injection because coronary spasm may well occur without *complete* occlusion or reproduction of symptoms. Nonocclusive spasm of the right coronary artery may well have occurred after the second or third dose of 0.05 mg of ergonovine maleate without reproduction of symptoms in the case report by Bauman. Repeat coronary angiography at that time might have averted the final larger dose of 0.2 mg that precipitated the unrelenting right coronary spasm.

5. The primary goal of therapy, after reproduction of Prinzmetal's angina and coronary spasm and its documentation, should be reversal of the coronary spasm because it is the presumed cause of the arrhythmias. We suggest administration of 1/100 grain of nitroglycerin sublingually, repeated once or twice over 5 minutes for unrelenting spasm. Intravenous nitroglycerin or nitroprusside can also be given if the spasm fails to resolve after 5 to 10 minutes.

6. Finally, we believe that reproduction of the clinical syndrome of Prinzmetal's angina during coronary angiography is worth the small risk because of the implications for long-term therapy with vasodilators. This is particularly true in view of the reported marked efficacy of calcium-antagonist drugs for this syndrome.[6–8]

John Speer Schroeder, MD, FACC
Coronary Care Unit
Cardiology Division
Stanford University School of Medicine
Stanford, California

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"NORMAL" CHOLESTEROL AND ATHEROSCLEROSIS

There is reason to question the basis of the definition of normal lipids used by Lie et al.[1] The issue is more than one of semantics, and potentially leads to an underestimate of the role of nutrition in the prevention of atherosclerosis. Cholesterol values for the group designated as "normolipemic" ranged from 214 to 291 mg/dl, whereas "hyperlipemic" patients had cholesterol values greater than 308 mg/dl. Using "normal" in a biologic sense,[2] not as an average or a statistical term, an international perspective would suggest that a cholesterol level much above 180 mg/dl is "abnormal" and leads to atherosclerosis on a wide scale.[3,4] It is worth noting that the lowest cholesterol value in a patient who came to surgery in this series was 214 mg/dl. Obviously the risk increases as cholesterol increases, but it would appear that a threshold can be defined. Lie et al. conclude that "the observation that microscopic changes of atherosclerosis may occur in saphenous vein grafts in some patients without hyperlipemia also emphasizes the importance of effective control not only of blood lipids but also of the other recognized risk factors for atherosclerosis." Although control of other risk factors is crucial in the hyperlipemic population in the United States, perhaps 214 to 291 mg/dl is not yet an optimal level of serum cholesterol, and should not be accepted as normal.

Richard Cooper, MD
Department of Community Health
Northwestern University
Chicago, Illinois

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REPLY

The point is well taken. Blood cholesterol and triglyceride concentrations of patients in our study were determined according to the procedures of the Lipid Research Clinics Program.[1] The "cut-off" values of cholesterol for patients in the 3rd, 4th, 5th and 6th decades were 210, 240, 260, and 280 mg/dl, respectively, as reported in a recent article by Gotto et al.[2] Cooper may be right in suggesting that perhaps 214 to 291 mg/dl is not yet an optimal level of cholesterol and should not be accepted as "normal" when regarded as a risk factor for atherosclerosis.

JT Lie, MD, FACC
Mayo Clinic
Rochester, Minnesota
Gerald M. Lawrie, MD, FACC
George C. Morris, MD, FACC
Baylor College of Medicine
Houston, Texas

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VENTRICULAR INVERSION WITHOUT TRANSPOSITION OF GREAT ARTERIES

Dunkman et al.[1] refer to "*d*-('complete') and *l*-('corrected')" transposition. No doubt, they are employing the widely used terminology coined by Van Praagh et al.[2,3] However, the accepted definition of "transposition" by Van Praagh et al.[2] is now "the anatomic condition in which the aorta arises from the morphologic right ventricle and pulmonary trunk from the morphologic left ventricle." This is not only the literal meaning of the term, but also the original meaning, as used by John Farre[4] of London in 1814. This definition is also accepted by the authors. While discussing the "loop rule," Dunkman et al. rightly point out that exceptions to it are not uncommon. Van Praagh[5] himself recognized its fallibility. Complete transposition with *d*- and *l*-transposition is well documented.[6,7] Conversely, corrected transposition with *d*- and *l*-transposition has been described.[8,9] To add to the confusion, situs inversus with D-ventricular loop and *l*-transposition,[10] and many such complex anomalies have been described. Therefore, the terms *d*- ('complete') and *l*-('corrected') transposition appear illogical to me.

A well known textbook of cardiology[11] defines *l*- and *d*-transposition thus: "*d*-transposition signifies that the aorta lies to the right of the pulmonary artery; *l*-transposition places the aorta to the left of the pulmonary artery." This does not take into account the connections of the great vessels to their respective chambers. In contrast, the term transposition indicates precisely that. It does not take into account the interrelation of the great vessels themselves. Use of the same term to indicate such vastly different meanings creates unnecessary confusion.

I believe this confusion can be avoided if the term transposition is strictly reserved to describe the ventriculo-arterial connection (discordance). To describe the relation between the pulmonary artery and aorta, *d*- and *l*-positions (not transposition) or *d*- and *l*-malpositions might be used (as D- and L-loop are used to describe the ventricular position). The term "anatomically corrected malposition" becomes more meaningful in this context. Similarly, the terms *o*-position, when the aortic valve is anterior[12] and *p*-position, when the aortic valve is posterior[3,13] may also be used.

In an otherwise excellent paper by Shinebourne et al.[14] and in the editorial by the same group[15] arguing forcefully in favor of a nomenclature based on connections rather than relations, the terms *l*- and *d*-transpositions are used. It is important to realize that connections and relations are different and to describe them separately. It was shown that an aorta normally related to the pulmonary artery can have an abnormal connection to the right ventricle.[2,13] A differentiation between transposition and position will increase understanding of the connections and relations.

Finally, I point out that a case of "anatomically corrected malposition" with an entirely subpulmonary conus has been reported.[16]

K. A. Chacko, MD
Department of Cardiology
Sree Chitra Tirunal Medical Centre
Trivandrum, India

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REPLY

If we interpret Chacko's letter correctly, he seems to take issue with our use of the term transposition and may suggest that the case we reported should be considered an example of anatomically corrected malposition of the great arteries.

We believe that our use of terms is in accord with the principles he endorses. Perhaps part of his concern arises from the fact that in both the original first page of his letter and its references [now corrected], he referred to the title of our article as "Ventricular inversion *with* (rather than *without*) transposition. . ."

We used the terms *d*-("complete") and *l*-("corrected") transposition because of their historical significance but without arguing that they are adequate to meet current taxonomic needs. We agree that transposition of the great arteries is best defined as that condition in which the aorta arises from the morphologic right ventricle and the pulmonary trunk from the morphologic left ventricle, and we accept the classification system recently outlined by Van Praagh[1] and by Stanger et al.[2]

Debate does persist as to whether isolated ventricular inversion (or discordance) should be retained as a separate nosologic entity or included with anatomically corrected malposition of the great arteries,[3-5] but even those who argue against its retention indicate that this issue is relatively unimportant provided atrioventricular and ventriculoarterial connections are identified.[5] Van Praagh[1] has retained isolated ventricular inversion (discordance) in his classification. Because of the entirely subpulmonary conus and location of the aorta rightward and posterior to the pulmonary artery, we believed that our case more closely resembled cases described as isolated ventricular inversion[7,8] than those identified as anatomically corrected malposition of the great arteries, which typically have a bilateral conus or, rarely, an entirely subaortic or absent conus and in which the aorta is usually anterior as well as to the right of the pulmonary trunk.[8-10]

It is not clear to us that the case cited by Chacko[9] as an example of entirely subpulmonary conus is such, because the echocardiogram in that case indicated the presence of a bilateral conus and the angiogram showed the aortic valve to be superior to the pulmonary valve, thus suggesting an at least partially subaortic conus. The authors reported that a "well-developed subpulmonary conus" was found at necropsy, but did not discuss the apparent discrepancy of this finding with the echocardiogram and angiogram, and the possible presence of some subaortic conus was not excluded.

W. Bruce Dunkman, MD
Cardiology Section
University of Pennsylvania Medical Service
Veterans Administration Hospital
Philadelphia, Pennsylvania

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ANTIARRHYTHMIC EFFECT OF VERAPAMIL

Elharrar et al.[1] report that verapamil is highly effective in suppressing ventricular arrhythmias induced by acute coronary ligation in open chest dogs. They seem to consider that this effect is essentially a result of a reduction in the extent of ischemia.

We doubt that this antiarrhythmic effect of verapamil is predominantly due to a reduction of the ischemic area rather than to its electrophysiologic action. In fact, the instantaneous effect of verapamil in antagonizing the ventricular extrasystoles of the early phase of acute human myocardial infarction[2,3] makes it improbable that this effect is mediated by a reduction in the extent of the ischemic area, a result that ought to require some time to verify. On the other hand, it has been observed that partially depolarized fibers of ischemic ventricular muscle show a "slow response" when activated. This response can produce an abnormal kind of automatic activity (rhythmic automatic depolarization) that is resistant to the usual antiarrhythmic drugs such as lidocaine and quinidine[4-7] but extremely sensitive to verapamil, a specific blocker of the "slow channel."

Thus, both clinical and experimental observations seem to indicate that in acute myocardial ischemia the electrophysiologic action of verapamil on slow responses is predominant in the antiarrhythmic effect of the drug as Zipes and his coworkers[8] have previously suggested.

Francesco Marchi
Arcispedale Di S. Maria Nuova
e Estabilimente Riuniti
di Firenze
Florence, Italy

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REPLY

The experimental data indicate that verapamil given before coronary occlusion in the dog reduces the extent of ischemia-induced conduction delay within the ischemic zone as well as the incidence of ventricular arrhythmias occurring within the first 6 minutes of coronary occlusion. This protective action of verapamil could be due to a direct action on cardiac cells in such a way that the time course and magnitude of the electrophysiologic alterations produced by myocardial ischemia result in less conduction delay and fewer arrhythmias. The protective effect could also be due to a reduction in the contractile performance or the metabolic requirement, or both, of the normal and ischemic myocardium.[1,2] The experimental model we used does not permit distinction between the relative contribution of each of these factors. When verapamil was given after occlusion of a coronary artery, it increased the extent of ischemia-induced conduction delay and the incidence of ventricular arrhythmias.[3]

We are hesitant to attribute the effects of verapamil on conduction in the ischemic zone only to an inhibition of the ability of the myocardial cell to generate slow channel-dependent action potentials because at present there is no direct evidence that such a response occurs during acute myocardial ischemia.[4] Because the extracell potassium in concentration

is elevated within the ischemic zone and because catecholamines are released from intraventricular sympathetic nerve terminals, it has been postulated that acute ischemia might be conducive to the genesis of slow channel-dependent action potentials.[5] Indeed, these conditions are somewhat similar to those required in vitro to induce the "slow responses." On the other hand, other factors such as hypoxia, acidosis and poor energy reserves, which undoubtedly are of importance during ischemia, tend to inhibit the genesis of the slow response.[6]

The analogy between the experimentally induced "slow response" and that which might occur during acute ischemia is limited because, in vitro, the primary alterations that occur are those of the extracell milieu whereas, during acute ischemia, the alterations of this milieu are secondary to alterations of the cell membrane. Thus, although some conditions during ischemia appear favorable to the genesis and maintenance of the "slow response," other factors may inhibit its development.

Nevertheless, if one assumes that slow channel-dependent action potentials are generated in the ischemic zone, and that they are responsible for the delayed and slow activation of that zone, then inhibition of the "slow response" by verapamil should result in a loss of activation of the ischemic zone and, therefore, in further deterioration of conduction at that site. On the contrary, verapamil increased the amplitude and decreased the time to onset of the electrogram recorded from the ischemic zone. Conceivably, verapamil might improve conduction by suppressing slow channel-dependent automaticity and restore maximal diastolic potential toward normal, but this is quite speculative. In fact, the conditions induced by acute myocardial ischemia may not be appropriate for the genesis of slow channel-dependent automaticity.[7]

Victor Elharrar, PhD
Winston E. Gaum, MD, FACC
Douglas P. Zipes, MD, FACC
Department of Medicine
Indiana University School of Medicine
Indianapolis, Indiana

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CRITERIA FOR MITRAL VALVE PROLAPSE

An interesting sequence of papers has recently appeared in this Journal. Smith et al.[1] reported an angiographic incidence of mitral valve prolapse of 43 percent in 336 consecutive patients undergoing left ventricular angiography. Six of these patients had clinical evidence of the click-murmur syndrome, and all six had echocardiographic evidence of mitral valve prolapse. The high percentage of patients who only had angiographic evidence for mitral valve prolapse led the authors to suggest that posterior bulging of the mitral valve on left ventricular angiography is not specific for mitral valve prolapse.

Two months later, Ruwitch et al.[2] approached the same problem but from the opposite perspective. They presented 12 patients who had angiographic evidence of posterior systolic motion of one or both mitral valve leaflets. Of this group, nine had no systolic click, and eight had echocardiograms that were reported as clearly negative for mitral valve prolapse. They concluded from these results that the clinical and echocardiographic manifestations of mitral valve prolapse lack the sensitivity of the ventricular angiogram. The correlation of the echocardiographic and clinical findings of mitral valve prolapse is not given in this paper. It would also be interesting to know what the frequency of angiographically determined mitral valve prolapse is in a random collection of angiograms from their institution.

In conclusion, it appears that the diagnosis of mitral valve prolapse lacks a gold standard. I agree with Smith et al. that before one can brand the echocardiogram as insensitive or alternatively brand the angiogram as nonspecific, more reliable criteria for the diagnosis for valve prolapse need to be established.

Jack D. Horton, MD
Division of Cardiology
Georgetown University Hospital
Washington, D. C.

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REPLY: I

We agree that mitral valve prolapse is indeed a disease "without a gold standard." At present, the *angiographic* criteria are possibly no more accurate a reflection of the anatomic abnormality of mitral valve prolapse than are the echocardiographic or, indeed, clinical criteria. The definitive information as yet unavailable is to what extent the angiographic criteria of mitral valve prolapse (or, for that matter, echocardiographic or clinical criteria) correlate with the pathologic findings. Unfortunately, even the pathologic abnormalities themselves are not well defined. Shrivastava et al.[1] in a recent excellent review of the pathology of mitral valve prolapse, leave little doubt that there is no clear-cut dividing line between the normal and abnormal mitral valve, on either the microscopic or the macroscopic level.

We agree with Smith et al. that posterior billowing of the mitral valve leaflets in systole is not necessarily specific for mitral valve prolapse. The majority of the patients described by Smith et al. had mild (grade I) mitral valve prolapse of a single scallop of the posterior leaflet, presumably the posterolateral scallop in most instances. We chose to exclude such patients in our study, believing that this "abnormality" represented either the normal left ventricular fornix or minimal (insignificant) bulging of the posterolateral scallop. If one excludes these cases from the series of Smith et al., the percentages of angiographic mitral valve prolapse associated with other conditions become substantially smaller and appear less likely to represent normal variation.

In our study, we did not deal with the sensitivity of the left ventriculogram relative to either the clinical manifestations or the pathology of mitral valve prolapse. Our goal was simply to select a small number of indisputably abnormal left ventriculograms and to evaluate the echocardiographic sensitivity for mitral valve prolapse in this highly selected group. Util-

izing only those angiograms in which the diagnosis of moderate or severe mitral valve prolapse was agreed upon by two expert angiographers independently, we believed that we had reliably excluded cases in which the diagnosis was borderline and possibly representative of normal variation. Although, in general, we adhered to the previously published angiographic criteria of mitral valve prolapse by Ranganathan et al.,[2] and Jeresaty et al.,[3] the lack of precise agreement even among such authorities as these leaves us unsure whether even clear-cut angiographic abnormalities, such as those in our study, reflect pathologically abnormal mitral valves.

Because only one echocardiogram in our study clearly indicated mitral valve prolapse, we had no data by which to correlate the echocardiographic and clinical findings in our study. The one echocardiogram that definitely demonstrated late systolic mitral valve prolapse was obtained in a 60 year old woman with hypertension and a normal electrocardiogram. Her physical examination revealed a grade I systolic ejection murmur, but no ejection click.

The prevalence of angiographically diagnosed mitral valve prolapse in a consecutive series of 686 patients undergoing left heart catheterization and angiography in this laboratory over the last year was 16.5 percent (113 patients). Six of these patients (0.9 percent) had coronary artery disease in addition. This rate is substantially lower than that cited by Smith et al., thus supporting our belief that our diagnostic criteria for "angiographic mitral valve prolapse" are appropriate and that we are not overdiagnosing the condition in the catheterization laboratory.

Joseph F. Ruwitch, Jr., MD
for
Alan N. Weiss, MD, FACC
Jerome L. Fleg, MD
Robert C. McKnight, MD
Philip A. Ludbrook, MD, FACC
Washington University School of Medicine
Saint Louis, Missouri

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REPLY: II

Horton has pointed out the apparent discrepancy between the results of our recent study and that of Ruwitch et al. concerning the diagnosis of mitral valve prolapse. We found posterior bulging of the mitral valve leaflet or leaflets to be an extremely common angiographic feature that occurred with similar frequency in all diagnostic subgroups. Because most of our patients had no clinical (auscultatory) or echocardiographic evidence of mitral prolapse, we concluded that the widely utilized angiographic criteria lack diagnostic specificity.

Conversely, Ruwitch and associates described 12 patients with angiographically "documented" mitral valve prolapse, 10 of whom had no mitral regurgitation, "most" of whom had no auscultatory abnormalities and 8 of whom had definitely normal echocardiograms. They concluded that echocardiography is an insensitive means of diagnosing mitral valve prolapse. Unfortunately, they did not provide information concerning the size of the total population from which this subgroup was derived, or the number of patients in the total population with clinical or echocardiographic evidence of mitral valve prolapse. These additional data might help explain the rather unusual characteristics of the subgroup described.

However, the discrepancy between the two reports may be more apparent than real. Thus, both in our initial report and in a subsequent prospective study,[1] we found that the prevalence of mitral valve prolapse varies markedly depending on the diagnostic criterion used. For instance, in our latter study, in which all patients had clinical, echocardiographic and angiographic studies, the prevalence of mitral prolapse ranged from 5 to 42 percent, depending on which "gold standard" was used. Obviously, if one accepts the angiographic appearance as the diagnostic standard (as did Ruwitch et al.), then both the clinical and echocardiographic criteria become insensitive indicators of the condition. Although we contend that currently utilized angiographic criteria lack specificity, we have infrequently found patients with both clinical and angiographic evidence of mitral valve prolapse who have a completely normal echocardiogram. Thus, we do agree with Ruwitch et al. that a normal echocardiogram does not positively exclude the presence of prolapse.

Horton's comments serve to highlight a major gap in our knowledge concerning this disorder. What is the clinical significance of end-systolic bulging of the mitral leaflet or leaflets discerned angiographically—particularly when such bulging is observed in the absence of mitral regurgitation, auscultatory abnormalities and echocardiographic features of prolapse? Until this has been established, or until a better "gold standard" has been defined, we believe that the diagnosis of mitral valve prolapse based solely on angiographic findings should be made with considerable caution.

Eldon R. Smith, MD
David B. Fraser, MD
Robert N. Anderson, MD, FACC
Dalhousie University
Victoria General Hospital
Halifax, Nova Scotia, Canada

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HEALTH PROMOTION AND PRIMARY PREVENTION

Borhani's critique[1] of the primary prevention of coronary heart disease illustrates a subtle point that our current nomenclature obscures. That is, among those who are ostensibly disease-free, for any given risk factor there are really two populations: those with the risk factor and those without. The term primary prevention is therefore too encompassing and needs to be replaced by (at least) two terms—"classic primary prevention" and "known-risk primary prevention." Although this division is frequently not clear-cut, it will facilitate the design of appropriate preventive strategies. For example, as Borhani observes, ". . . it is much easier not to start smoking than to stop." Thus, primary prevention in the area of smoking would involve two thrusts: one directed toward smokers and another toward nonsmokers. In general, it would seem best to direct primary prevention efforts toward those with fewer risk factors. This would also allow a positive emphasis on health promotion rather than on the more negative concept of disease prevention.

Harry P. Wetzler, MD
San Antonio, Texas

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REPLY

The point on emphasis of the health promotion concept is well taken. However, the problem is not with the term primary prevention; rather, it is with the application of the concept of primary prevention to coronary heart disease. There seems to be no argument that for primary prevention to be effective in the area of smoking, it should begin in childhood.

Nemat O. Borhani, MD, FACC
Department of Community Health
University of California, Davis
Davis, California

CARDIOLOGY IN CHINA REVISITED

In 1972 I reported on the status of cardiology in the People's Republic of China.[1] This letter provides an update of the report based on the developments I have observed on several more recent visits to China.

Coronary artery disease: This is still the second most common cardiovascular disease in China, as it was in 1973. In a recently completed survey the prevalence rate of asymptomatic coronary heart disease among the Chinese peasants, who constitute more than 80 percent of the total population in China, was 3 to 5 percent. The geographical differences, which I noted earlier,[2] remain unexplained: 3.5 percent (persons over 30 years of age) in Wuhan; 4 percent (persons 30 to 88 years) in Szechuan; 4.2 percent (persons 40 to 69 years) in Shanghai; 5.4 percent (persons over 40 years) in Liaoning; and 7.75 percent (persons over 40 years) in Canton.

Selective coronary arteriography was introduced in China in 1973 and has become an accepted procedure in the diagnosis and management of coronary artery disease. However, coronary bypass surgery, which was first performed in Canton in May 1975, is still not widely used in China as a definite therapeutic measure.

The emphasis in coronary artery disease is clearly on prevention and early detection. Hypertension, which has shown an increase among the Chinese during the last 2 decades, remains the most important risk factor in coronary artery disease.[1] Many hospitals in China have established hypertension control bases in factories and communes and conducted mass surveys. Other risk factors include cigarette smoking, hypercholesterolemia and diabetes. The 6 year incidence rate for development of coronary artery disease among Chinese persons who are 45 years of age, do not smoke, have a systolic blood pressure of 120 mm Hg, serum cholesterol level of 185 mg/dl, and a normal electrocardiogram, and are nondiabetic, is 1.6 percent in men and 0.6 percent in women. For Chinese of the same age who smoke, have a systolic blood pressure of 195 mm Hg, a serum cholesterol value of 335 mg/dl, electrocardiographic findings of left ventricular hypertrophy and diabetes, the 6 year incidence rate is 46.3 percent in men and 13.2 percent in women.[3]

In mass surveys and in the clinical diagnosis of coronary artery disease the Chinese use the Master's two-step test and, more recently the treadmill tests. Propranolol has been successfully used to differentiate the false positives from the true positives exercise test, the latter showing persistent ST-T changes after exercise 1 1/2 to 2 hours after administration of 20 mg of oral propranolol.[4] This test has been extremely useful in middle-aged Chinese women, who have a rather large incidence of false-positive treadmill electrocardiographic tests.

Coronary care units, practically nonexistent in 1972, are now established in most hospitals in China. Although they are less sophisticated than those in the United States, they are adequate and up to modern standards. For those who may not appreciate the current state of the art in the treatment of acute myocardial infarction in China, I recommend the eyewitness account[5] of an American doctor who, while traveling in China in 1975, had a massive acute myocardial infarction compli-

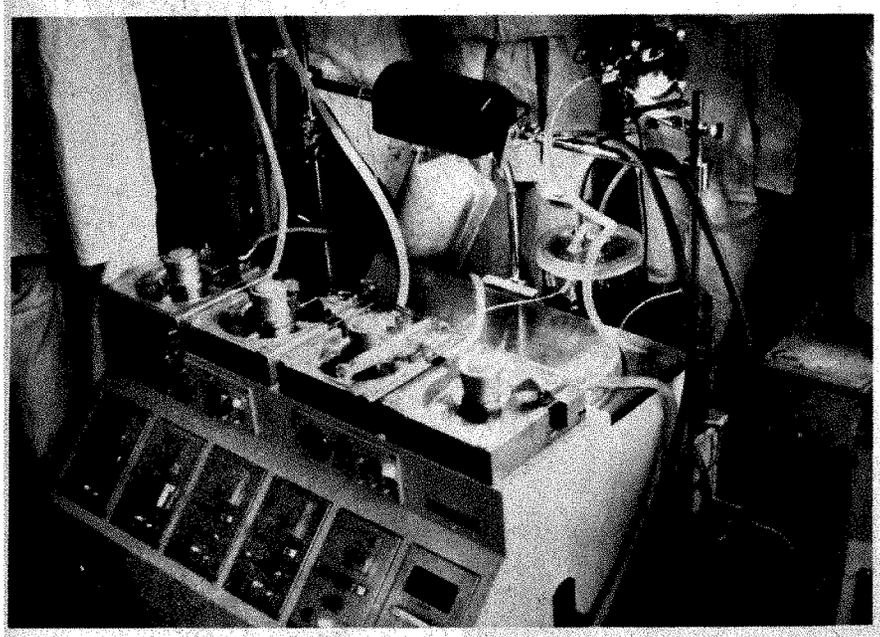


FIGURE 1. Disposable bubble oxygenator for open heart surgery made and used in the Shanghai Third People's Hospital, Shanghai, China.

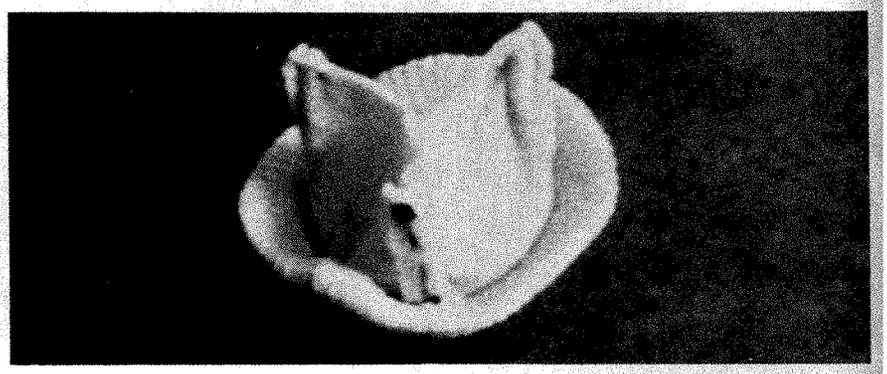


FIGURE 2. Calf pericardial xenograft made and used in Fu Wai Hospital, Peking, China.

cated by ventricular fibrillation and congestive failure and who has completely recovered.

Cardiac surgery: Acupuncture anesthesia, which was first used during an open heart operation in the Shanghai Third People's Hospital on April 19, 1972, is still an important technique. Up to July 14, 1977 a total of 196 cases of congenital and acquired heart disease had been successfully operated on in that hospital. The disc oxygenator used in 1972 has been replaced by a disposable bubble oxygenator (Fig. 1). Many technological advances have also been made in the field of cardiovascular prostheses and cardiac pacemakers (Fig. 2 and 3).

Idiopathic hypertrophic subaortic stenosis: This condition, which was not well known in 1972, is being diagnosed more frequently, apparently because of the heightened index of suspicion and the availability of echocardiography. Although the term asymmetric septal hypertrophy has already crept into Chinese medical reports, hypertrophic cardiomyopathy is the preferred term. The Chinese emphasize the importance of early detection and diagnosis in management of patients with this condition, because in recent years it has been found to be an important cause of sudden death in young adults in China.

The click-murmur syndrome of mitral valve prolapse: This syndrome is also being increasingly recognized in China. In a coronary survey conducted by the First Affiliated Hospital of Sian Medical College in Sian in 1977, 6 subjects with click-murmur syndrome were found among 2,060 asymptomatic persons—an incidence rate of 0.3 percent. All six subjects were men. In the United States, the asymptomatic occurrence of this syndrome is predominantly in young women.[6,7] However, the difference is probably due to a sampling difference. That some of these six may have coronary artery disease is suggested by another interesting observation: Among 98 patients admitted to the same hospital with coronary artery disease during the past 3 years, the click-murmur syndrome was found in 3. This finding by my Chinese colleagues lends further support to my long-held belief that coronary heart disease is not an uncommon cause of click-murmur syndrome.[8,9] Ascertainment of the true incidence of the click-murmur syndrome among the Chinese must await the result of a mass survey.

Research and exchange of data: During my most recent visit in late 1977, in contrast to earlier visits, I observed a renewed emphasis on basic research and interest in modern technology. The educational system has also undergone a big change since my last report in 1975.[10] The curriculum in medical schools in China has now been extended from 3 to 5 years and there is more emphasis on basic sciences. The examination system, which was abolished between 1973 and

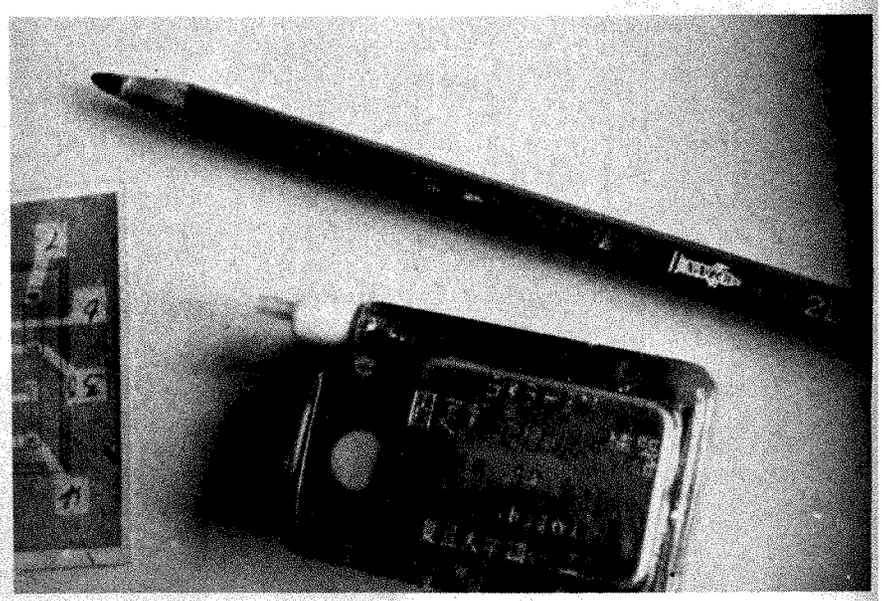


FIGURE 3. Implantable fixed-rate cardiac pacemaker made in the Futan University, Shanghai, China.

1976, was reintroduced toward the end of 1977. The Chinese Medical Association, dormant for several years, has just reconvened a national meeting and is interested in further international exchanges, especially with the United States. After the reappearance of the *Chinese Medical Journal* in January 1973,[11] the *Chinese Journal of Internal Medicine* and the *Chinese Journal of Surgery* have also resumed publication. I am confident that in the years to come there will be an ever increasing exchange of information between the Chinese and American medical professions from which both will profit. As the late Dr. Paul White said, "medicine is the world's best diplomat."

Tsung O. Cheng, MD, FACC
Division of Cardiology
Department of Medicine
George Washington University
Washington, D.C.

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Congestive Heart Failure and Cardiac Impedance, by Michael C. Ritota, MD. Newark, New Jersey, M.E.D.S., 1978, 106 pages

Coronary Artery Surgery, by John L. Ochsner, MD and Noel L. Mills, MD. Philadelphia, Lea & Febiger, 1978, 275 pages, $25.00

Coronary Bypass Surgery, edited by Shahbudin H. Rahimtoola, MB. Philadelphia, F. A. Davis, 1977, 287 pages, $35.00

Diagnostic Pointers in Clinical Electrocardiology, by Leo Schamroth, MD. Bowie, Maryland, Charles Press, 1978, 268 pages

Disturbances in Lipid and Lipoprotein Metabolism, edited by John M. Dietschy, Antonio M. Gotto, Jr. and Joseph A. Ontko. Bethesda, Maryland, American Physiological Society, 1978, 295 pages, $25.00

Echocardiography: Interpretation and Diagnosis, by Jack J. Kleid, MD and Stephen B. Arvan, MD. New York, Appleton-Century-Crofts, 1978, 460 pages

Electrocardiology-1, edited by M. J. Gandhi, MD, A. B. Mehta, MD and D. B. Pahlajani, MD. Bombay, India, Tata Press, 1975, 244 pages

From Cardiac Catheterization Data To Hemodynamic Parameters, by Sing San Yang, MD, Lamberto G. Bentivoglio, MD, Vladir Maranhao, MD and Harry Goldberg, MD. Philadelphia, F. A. Davis, 1978, 527 pages, $25.00

Gross Anatomy Dissector: A Companion for Atlas of Clinical Anatomy, by Richard S. Snell, MD, PhD. Boston, Little, Brown, 1978, 358 pages, $9.95

Heart Disease in Infancy and Childhood, third edition, by John D. Keith, MD, Richard D. Rowe, MD and Peter Vlad, MD. New York, Macmillan, 1978, 1083 pages, $50.00

Hypertension: Mechanisms, Diagnosis and Treatment, edited by Gaddo Onesti, MD and Albert N. Brest, MD. Philadelphia, F. A. Davis, 1978, 333 pages, $35.00

Living With High Blood Pressure. The Hypertension Diet Cookbook, by Joyce Daly Margie, MS and James C. Hunt, MD. Bloomfield, New Jersey, HLS Press, $12.95, 1978

Management of Essential Hypertension, by F. Gilbert McMahon, MD. Mount Kisco, New York, Futura Publishing, 1978, 468 pages, $18.50

A Manual of Thoracic Surgery, by Arndt von Hippel, MD. Springfield, Illinois, Charles C Thomas, 1978, 247 pages, $13.75

The Mechanics of the Circulation, by C. G. Caro, T. J. Pedley, R. C. Schroter and W. A. Seed. New York, Toronto, Oxford University Press, 1978, 527 pages, $46.00

New Trends in Venous Diseases, by A. Kappert, MD. Bern, Switzerland, Hans Huber, 1977, 309 pages

The Pacemaker and Valve Identification Guide, by Dryden Morse, MD and Robert M. Steiner, MD. Garden City, New York, Medical Examination Publishing, 1978, 116 pages, $40.00

Practical Echocardiography. A Basic Manual, by C. David Joffe, MD. Bowie, Maryland, Charles Press, 1978, 193 pages, $16.95

The Practice-Oriented Medical Record, by Gerald S. Lang and Kenneth J. Dickie. Germantown, Maryland, Aspen Systems, 1978, 287 pages, $19.75

Principles of Cardiovascular Nuclear Medicine, edited by B. Leonard Holman, MD, Edmund H. Sonnenblick, MD and Michael Lesch, MD. New York, San Francisco, London, Grune & Stratton, 1978, 246 pages

Renin, Vol 2, by Suzanne Oparil and Richard Katholi. Montreal, Quebec, Canada, Eden Press, 1977, 332 pages, $24.00

A Self-Teaching Atlas of Echocardiography, by Charles Z. Naggar, MD. Bowie, Maryland, Charles Press, 1978, 275 pages

Transplant: A Family Chronicle, by Philip Dossick. New York, Viking Press, 1978, 271 pages, $10.95

Very Early Recognition of Coronary Heart Disease, edited by Lawson McDonald, MD, John Goodwin, MD and Leon Resnekov, MD. Amsterdam-Oxford, Excerpta Medica, 1978, 194 pages, $32.75

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

OCTOBER 1978 THROUGH DECEMBER 1978

To be arranged individually Preceptorships in Cardiology. Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

OCT. 12–14 **Cardiology Update—1978.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt House, Monterey, CA

OCT. 13–14 **Geriatric Cardiology. Physiologic vs. Pathologic Aging of the Cardiovascular System: Clinical Applications and Therapeutic Considerations.** Borys Surawicz, FACC and Raymond Harris, FACC, directors. Hyatt Regency Lexington, Lexington, KY

OCT. 18–20 **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. Waldorf-Astoria Hotel, New York, NY

OCT. 19–21 **Valvular Disease—Practical Diagnosis and Management.** Peter C. Gazes, FACC, director and Charles P. Summerall III, FACC, Grady H. Hendrix, FACC, William H. Barnwell II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, Jr. and Robert G. Irvin, co-directors. Kiawah Island Inn, Kiawah Island, Charleston, SC

Nov. 2–4 **New Techniques and Concepts in Cardiology. Coronary Artery Disease: Noninvasive Diagnosis, Cardiac Rehabilitation, Pharmacologic Treatment, Control of Risk Factors and Role of Surgery.** Stephen E. Epstein, FACC, director, Hyatt Regency Hotel, Washington, DC

NOV. 6–15 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

DEC 2–4 **Advances in Heart Disease 1979.** Dean T. Mason, FACC, director, Fairmont Hotel, San Francisco, CA

DEC. 3–6 **Coronary, Hypertensive, Valvular and Myocardial Heart Diseases: The Multidisciplinary Approach.** William C. Roberts, FACC, director, The Williamsburg Conference Center, Williamsburg Lodge, Williamsburg, VA

DEC. 8–10 **Eleventh Annual Cardiovascular Symposium: Patient Oriented Management of Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, NY

DEC. 11–14 **Core Curriculum: Interpretation and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, directors. Philadelphia Marriott Motor Hotel, Philadelphia, PA

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

OCTOBER THROUGH DECEMBER 1978

Month/Dates	Course Director	Title of Program
September 25–27	Kenneth M. Rosen, MD, FACC	**Evaluation of Arrhythmias with His Bundle Recording and Cardiac Stimulation**
October 4–6	Charles E. Rackley, MD, FACC	**Clinical Evaluation and Treatment of Coronary Artery Disease**
October 19–21	Pravin M. Shah, MD, FACC	**Adult Echocardiography: Clinical Applications–M-Mode vs 2-Dimensional**
October 23–25	Douglas P. Zipes, MD, FACC	**The Ubiquitous PVC: Sorting Out the Dilemma**
November 6–9	Ralph Shabetai, MD, FACC	**Pericardial and Myocardial Diseases: Identification, Interaction, and Clinical Significance**
December 4–6	Borys Surawicz, MD, FACC	**Advanced Cardiac Electrophysiology and Electrocardiography**
December 11–13	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**

28th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Miami Beach, Florida **March 11–15, 1979**

- **Technical Exhibits**
  Deadline for requests for space: October 2, 1978
- **Scientific Exhibits**
  Deadline for requests for space: October 2, 1978
- **Young Investigators' Awards Competition**
  Entries must be postmarked no later than November 1, 1978

For application forms, write Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

AMERICAN COLLEGE OF CARDIOLOGY

Announces . . .

AFFILIATE IN TRAINING MEMBERSHIP

For Physicians in Cardiovascular Related Training Programs

Candidates for this membership category must be current full-time trainees in a recognized cardiovascular (adult, pediatric, surgical) related program in fulfillment of requirements for admission to a subspecialty board examination which holds membership in the American Board of Medical Specialties. Upon completion of training and in order to maintain an affiliation with the College, the members are encouraged to apply to the Credentials Committee for status in one of the other three membership categories.

The application for Affiliate in Training must be signed by the Director of the applicant's training program and two sponsors, both of whom must be Fellows of the College. One of the sponsors may be the Director of the training program, provided he is a Fellow of the College. The annual dues for an Affiliate in Training are $25.00.

Advantages to the Affiliate in Training

1. Subscription to *The American Journal of Cardiology,* the official journal of the College.
2. Reduced fees for all educational programs of the College.
3. Preference for enrollment in programs sponsored by the College with a limited registration.
4. Receipt of the quarterly publication, *Cardiology,* the newsletter of the College.
5. Participation in all affairs of the College as a member rather than as a guest of the College.

Those desiring an application form should write to Ms. Margaret E. Coffey, Director, Membership Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

INSTRUCTIONS FOR AUTHORS

The editors of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles devoted to cardiovascular disease. Articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY and become the property of the Publisher. The Publisher reserves copyright and renewal on all published material, and such material may not be reproduced in any form without the written permission of the Publisher. Statements in articles are the responsibility of the authors. Authors will assist the editors in the prompt processing of manuscripts if these instructions are followed:

THE WHOLE PAPER

- Address manuscript to Managing Editor, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- Submit two copies of all elements of the article: text, references, legends, tables and figures.
- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
- Type all matter: (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on one side of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

THE TITLE PAGE

- Include first names, degrees and, where applicable, FACC for all authors.
- Provide a short running title of 3 to 6 words.
- Insert at bottom: name and address of institution from which work originated plus information about grants.
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- Limit words as follows: 100 to 250 words for major articles; 50 to 100 words for case reports.
- Add at end of abstract: list of 2 to 6 key words and subjects for indexing.

THE TEXT

- Type in duplicate; double-space.
- Do not use abbreviations such as SVC, WPW: write out superior vena cava, Wolff-Parkinson-White.
- Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.
- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
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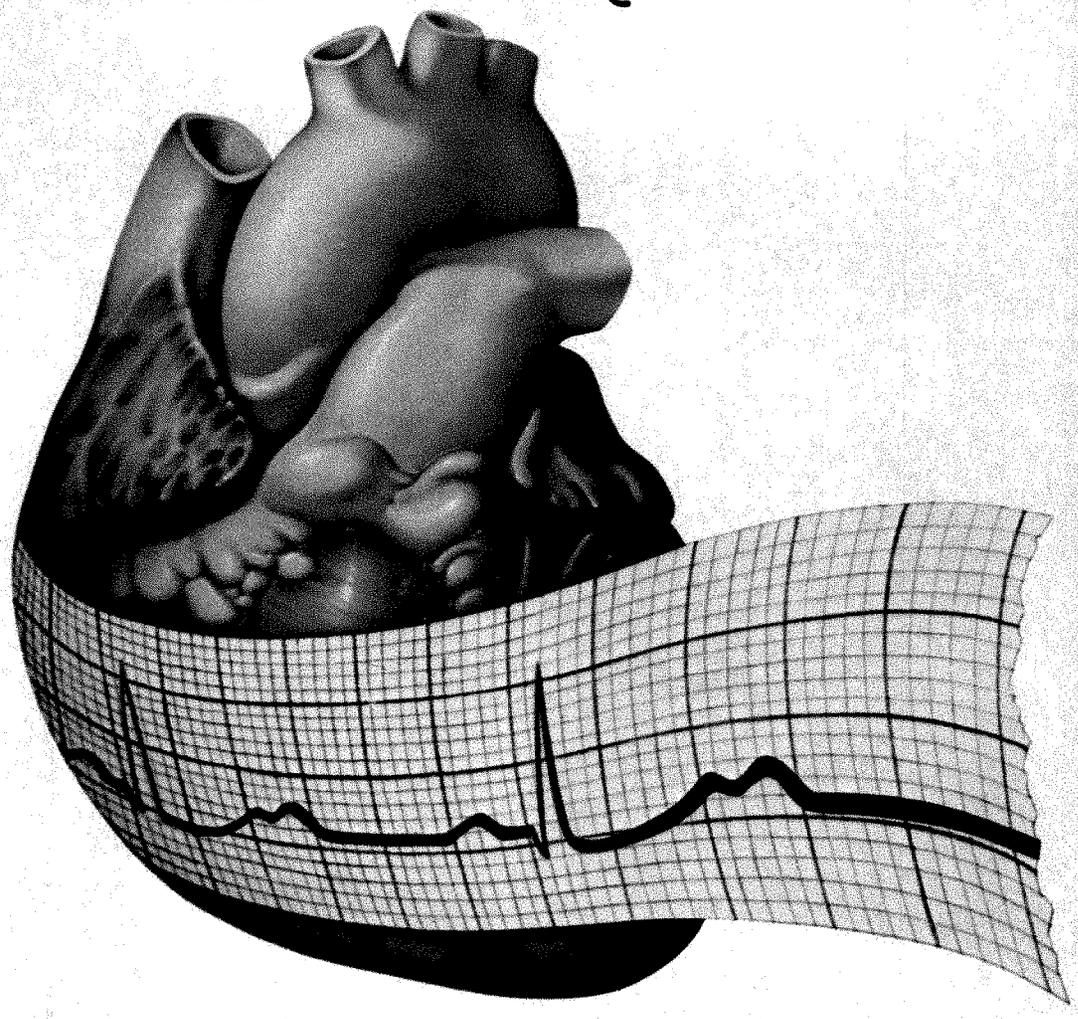
28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

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CONVENIENT AND ECONOMICAL

KAON-CL 20%®

(potassium chloride) LIQUID

40 mEq per 15 ml

Indications: KAON-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. KAON-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: In patients with hyperkalemia, chronic renal failure, systemic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Warnings: Do not administer full strength. KAON-CL 20% will cause gastrointestinal irritation if administered undiluted.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

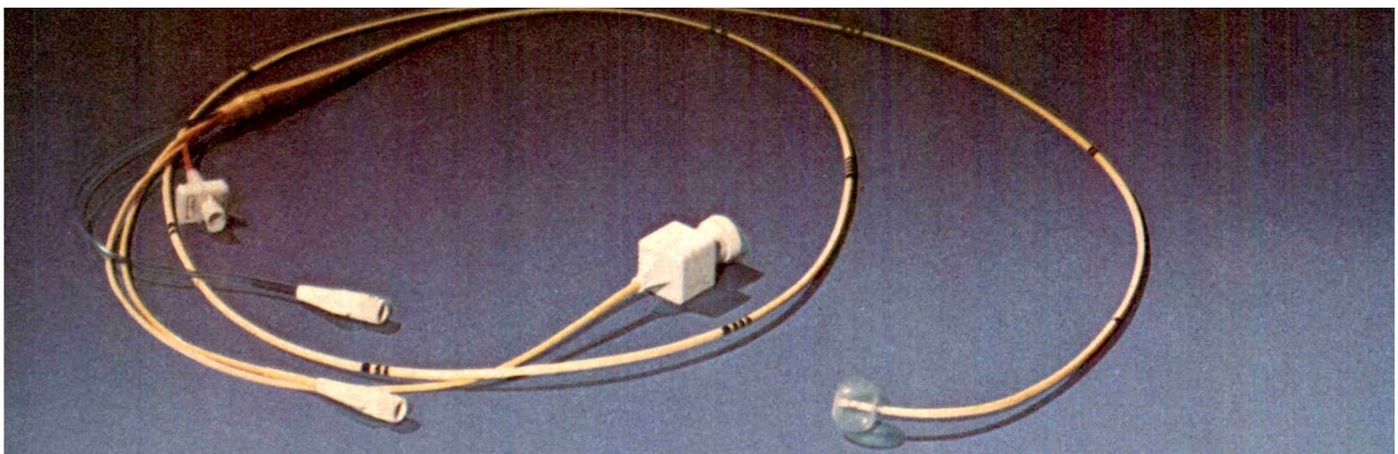
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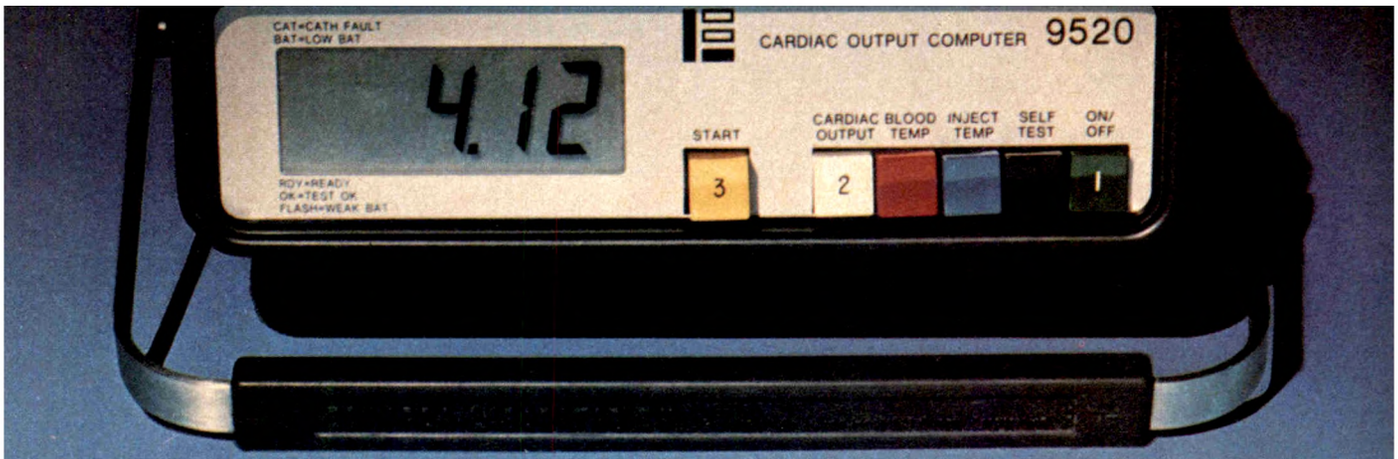
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The SWAN-GANZ Flow-Directed Catheter was the original idea and is now the most widely used catheter of its kind in the world. The Edwards Cardiac Output Computer was also a first. Now in its fourth generation, it is highly regarded for its simplicity of operation, state-of-the-art electronics, and compact, portable size. Each has been designed for the other, to assure system reliability and performance.

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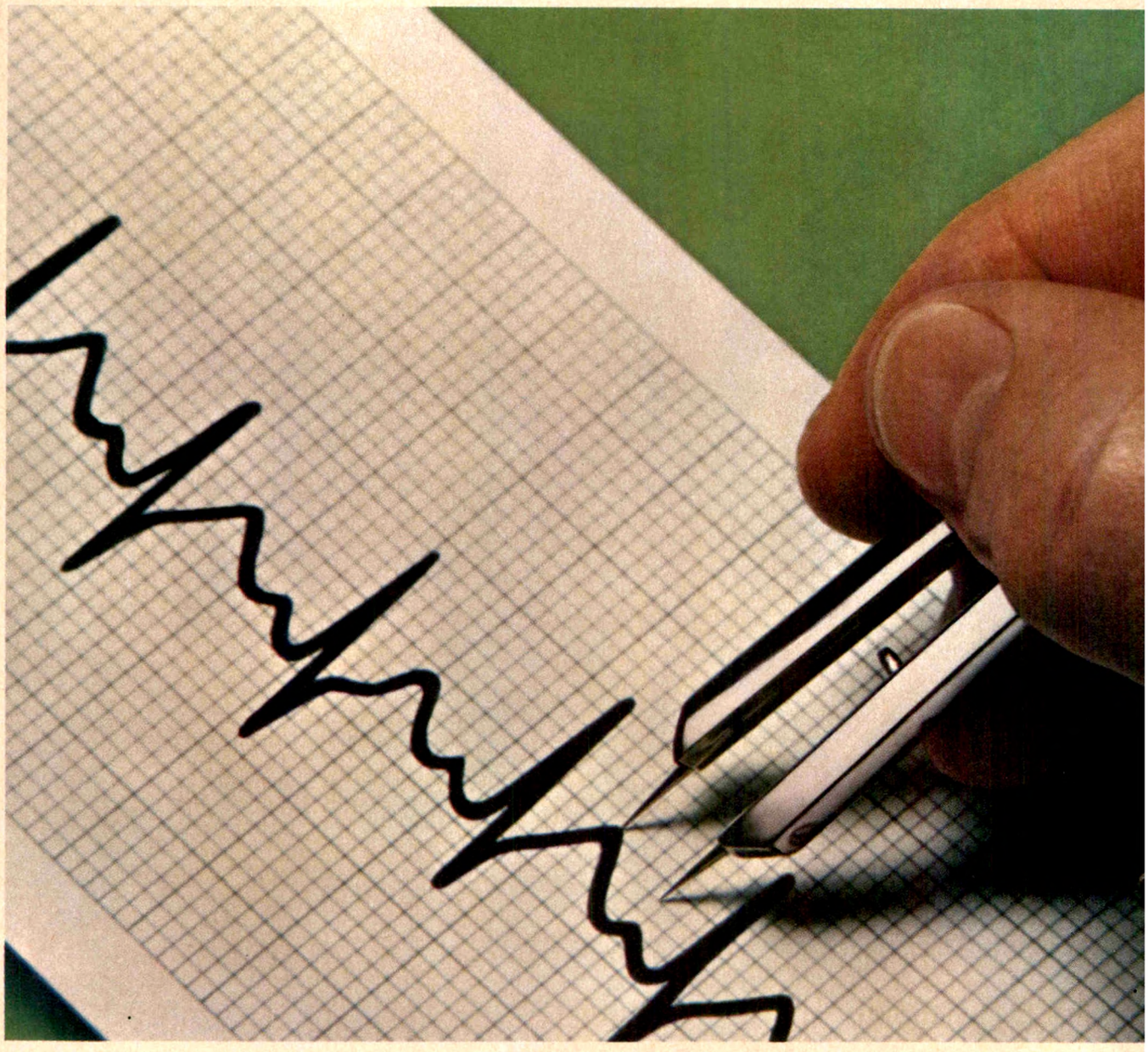
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INDERAL®
(propranolol hydrochloride)
PERFORMANCE IN CARDIAC ARRHYTHMIAS

EFFECTIVE ALONE OR IN COMBINATION



A106

INDERAL (propranolol hydrochloride): Successful treatment of supraventricular arrhythmias for over 10 years

INDERAL, used alone or in combination with other antiarrhythmics, has improved or resolved a variety of supraventricular arrhythmias.[1-7]

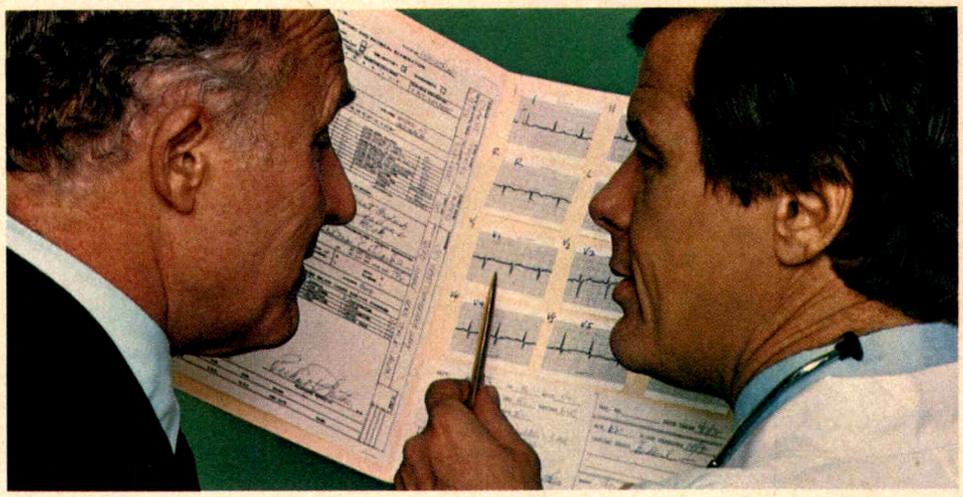
INDERAL alone: Results of use against atrial tachyarrhythmias in one series have recently been reported:

Arrhythmia	Patients	Proportion deriving benefit	
		Complete	Partial
Sinus tachycardia	86	59%	22%
Atrial tachycardia (including paroxysmal type)	154	61%	19%
Atrial flutter	50	54%	32%
Atrial fibrillation	139	53%	26%

Adapted from Coodley and Snyder.[8]

INDERAL is particularly effective in therapy of supraventricular tachyarrhythmias.[9] It slows depolarization of sinus and ectopic pacemaker cells, and retards impulse-conduction in the atria and across the AV node.[1,10,11] In cases where it cannot restore normal sinus rhythm, INDERAL is frequently effective in reducing the ventricular rate.[1-3,12-14] INDERAL may prevent recurrent supraventricular tachyarrhythmias when digitalis and quinidine fail to do so.[9,12] In addition, INDERAL is a useful short-term adjunct for arrhythmias of thyrotoxicosis, when





used with specific therapy. Since INDERAL may mask the clinical signs of hyperthyroidism, abrupt withdrawal should be avoided to prevent exacerbation of the symptoms of hyperthyroidism.

And in combination: INDERAL has also been used to complement the actions of other antiarrhythmic agents.[3-5,8,9,13] The combination of INDERAL and quinidine has suppressed supraventricular arrhythmias that have not responded to either drug alone.[3,9]

When toxic doses of digitalis glycosides occasionally fail to control the ventricular rate in patients with atrial fibrillation or flutter, addition of INDERAL to a digitalis glycoside, with reduction of the digitalis dosage, may prolong AV conduction to the point where satisfactory control of ventricular rhythm is established.[8,15]

INDERAL: Often effective in tachyarrhythmias of digitalis intoxication[2,9,10,14] INDERAL has been found useful in the treatment of certain digitalis-induced arrhythmias that persist following discontinuation of digitalis and correction of electrolyte disturbances, particularly hypokalemia. Its use in this setting may be limited by the presence of significant congestive failure or heart block, and the development of severe bradycardia. (Please see prescribing information on the next page for "Overdosage or Exaggerated Response.")

INDERAL is contraindicated in sinus bradycardia, greater than first degree heart block, and congestive heart failure unless the failure is secondary to tachyarrhythmias treatable with INDERAL. (See prescribing information for complete list of CONTRAINDICATIONS.)

Please see next page for prescribing information.

Ayerst

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

INDICATIONS: Cardiac Arrhythmias:

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.

May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use **INDERAL (propranolol hydrochloride) unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.**

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors); and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn. b) If tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL (propranolol hydrochloride) is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE: At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS: Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.*, electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE:

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

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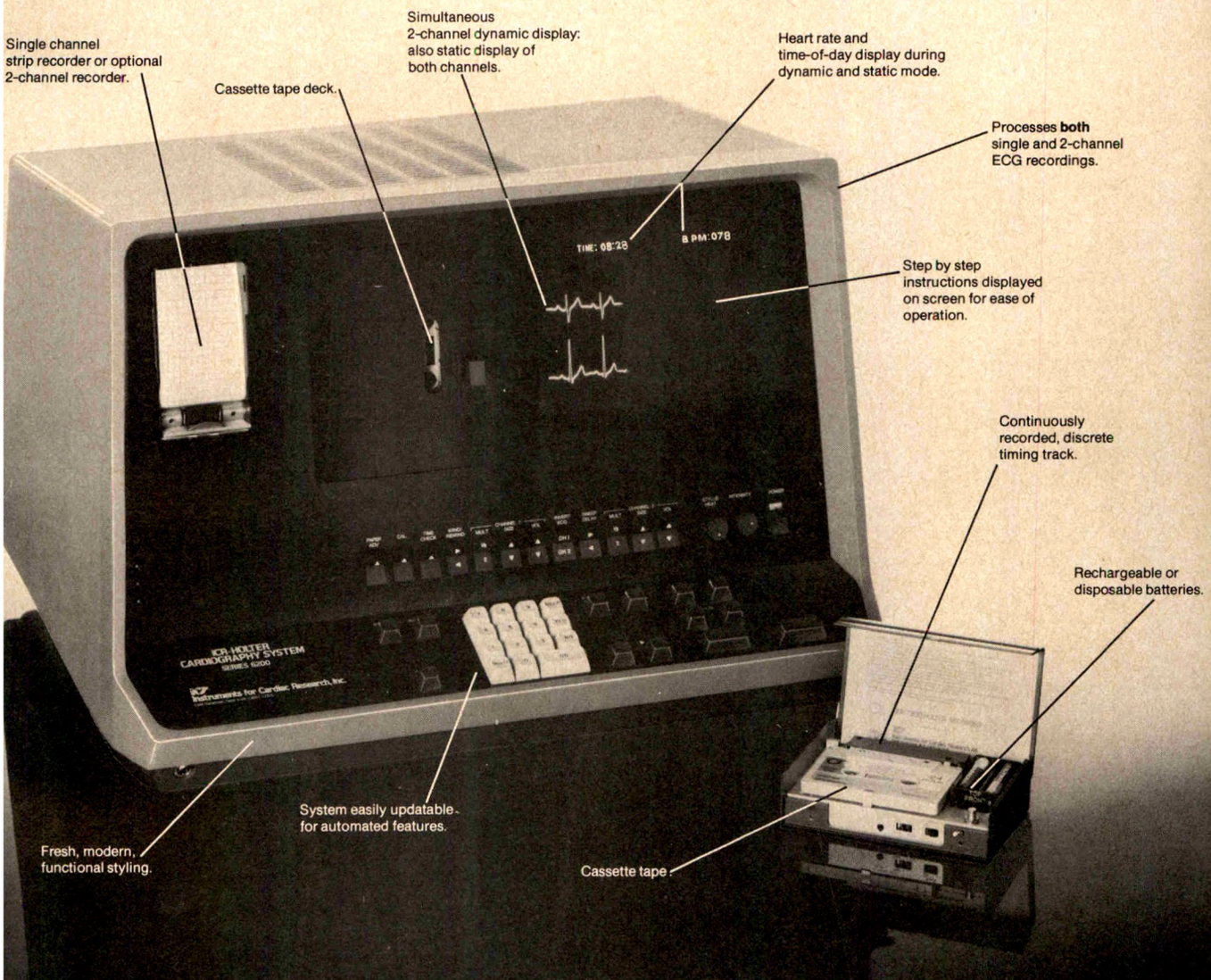
No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCES: 1. Shand, D.G.: N. Engl. J. Med. *293*:280 (Aug. 7) 1975. 2. Conn, R.D.: Postgrad. Med. *55*(No. 2):131 (Feb.) 1974. 3. Fors, W.J., Vanderank, C.R., and Reynolds, E.W.: Am. J. Cardiol. *27*:190 (Feb.) 1971. 4. Levi, G.F., and Proto, C.: Cardiology *55*:249, 1970. 5. Stern, S.: Am. Heart J. *74*(No. 2):170 (Aug.) 1967. 6. Luna, M.H., Adelson, E.I., and Miller, A.J.: Circulation *34*:767 (Nov.) 1966. 7. Gianelly, R.E., Griffin, J.R., and Harrison, D.C.: Ann. Intern. Med. *66*:667 (Apr.) 1967. 8. Coodley, E.L., and Snyder, S.: Am. Fam. Physician *14*(No. 5):146 (Nov.) 1976. 9. Miller, R.R., Amsterdam, E.A., and Mason, D.T.: Drug Therapy *5*:110 (Feb.) 1975. 10. Danahy, D.T., and Aronow, W.S.: Postgrad. Med. *61*(No. 1):113 (Jan.) 1977. 11. Gettes, L.S.: Med. Opinion *5*(No. 9):19 (Sept.) 1976. 12. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 13. Michaelson, S.P., and Wolfson, S.: Cardiovasc. Med. *1*(No. 3):213 (Nov.) 1976. 14. Wit, A.L., Hoffman, B.F., and Rosen, M.R.: Am. Heart J. *90*(No. 5):665 (Nov.) 1975. 15. Bigger, J.T., and Giardina, E.G.V.: Cardiovasc. Clin. *6*(No. 2):103, 1974.

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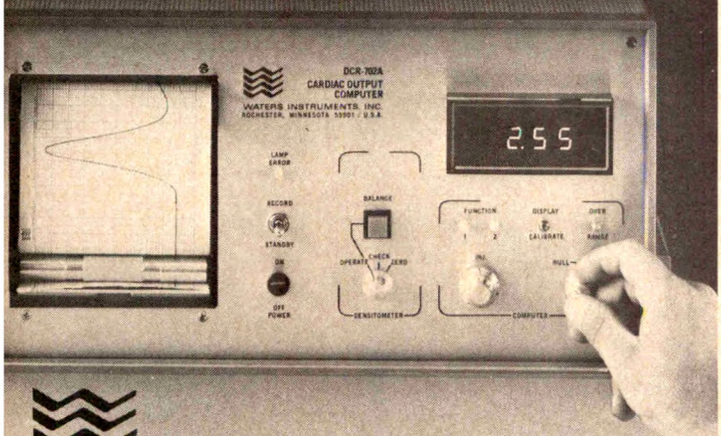
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DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amid analogue of procaine hydrochloride and is available for oral adminis tration as capsules and veneer-coated tablets providing 250 mg., 37 mg., and 500 mg. procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where hypersensitivity to procainamide exists; bear in mind cross sensitivity t procaine and related drugs. Should not be given to patients with com plete atrioventricular heart block. Contraindicated in cases of secon degree and third degree A-V block unless an electrical pacemaker i operative.

ADMINISTRATION: Should procainamide therapy be continued for an appreciable period, electrocardiograms should be made occasionally t determine its further need.

PRECAUTIONS: Evidence of untoward myocardial response should b carefully watched for in all patients. In the presence of myocardial dam age with atrial fibrillation or flutter, the ventricular rate may increas suddenly as the atrial rate is slowed; adequate digitalization reduces bu does not abolish this danger. Ventricular tachysystole is particularl hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode ma occur in correcting atrial fibrillation due to the forceful contractions o the atrium.

Extreme caution is required in attempting to adjust the heart rate whe ventricular tachycardia has occurred during an occlusive coronary ep sode or where the use of procainamide may result in additional depres sion of conduction and ventricular asystole or fibrillation as in secon degree and third degree A-V block, bundle branch block, or sever digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients wit severe organic heart disease and ventricular tachycardia that complet heart block, which may be difficult to diagnose, may be present. Sinc asystole may result if the ventricular rate is significantly slowed withou attainment of regular atrioventricular conduction, procainamide shoul be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage ma produce symptoms of overdosage—principally ventricular tachycardi and severe hypotension.

A syndrome resembling lupus erythematosus has been reported wit maintenance procainamide therapy. Common symptoms are polyarth ralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleura effusion and pericarditis may also occur. Rare cases of thrombocyto penia or Coombs-positive hemolytic anemia, possibly related to thi syndrome, have been reported. Measure anti-nuclear antibody titers a regular intervals in patients on procainamide for extended periods o time or in whom symptoms suggestive of lupus-like reaction appear; i event of rising titer (anti-nuclear antibody) or clinical symptoms of LE assess the benefit/risk ratio related to continued procainamide therap (see boxed Warning). Steroid therapy may be effective if discontinuatio of procainamide does not cause remission of symptoms. If the syndrom develops in a patient with recurrent life-threatening arrhythmias no otherwise controllable, steroid-suppressive therapy may be used con comitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration Serious disturbances of cardiac rhythm such as ventricular asystole o fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been re ported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasion ally reported following repeated use of the drug, and deaths have oc curred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be in structed to report any soreness of the mouth, throat, or gums, unex plained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appro priate treatment should be instituted immediately. Bitter taste, diarrhea weakness, mental depression, giddiness, psychosis with hallucinations and hypersensitivity reactions such as angioneurotic edema and macu lopapular rash have been reported.

The package insert should be read carefully to become familiar wit the recommended dosage for the indicated conditions and for full pre scribing information.

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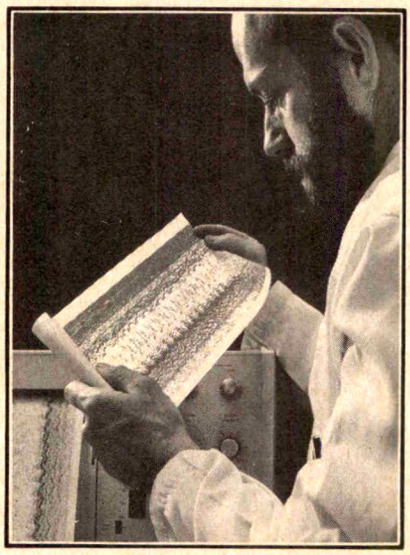
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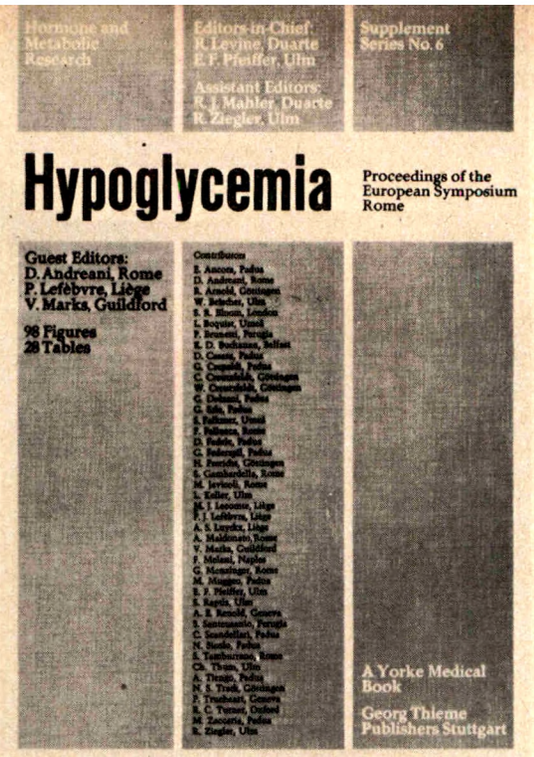
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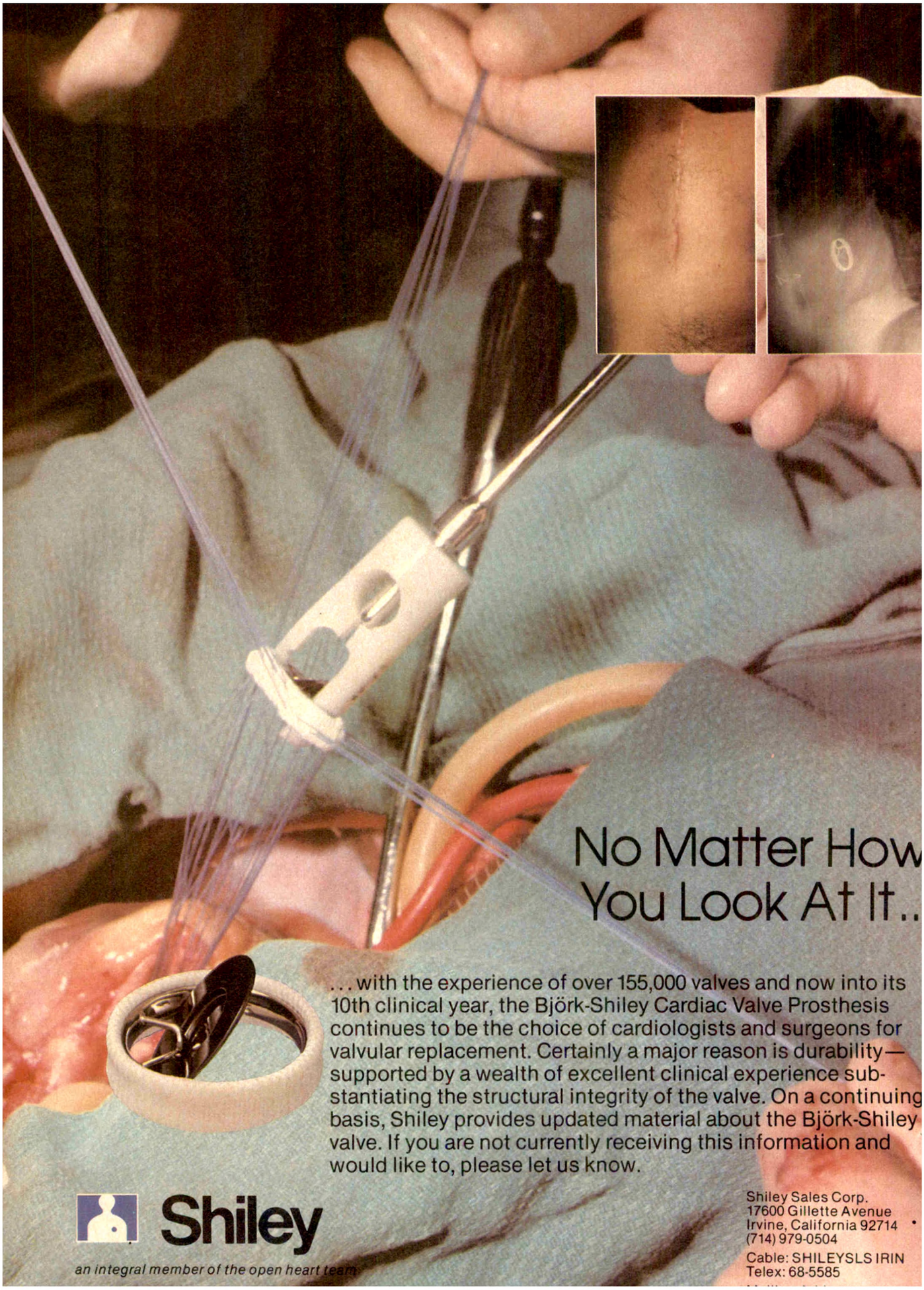
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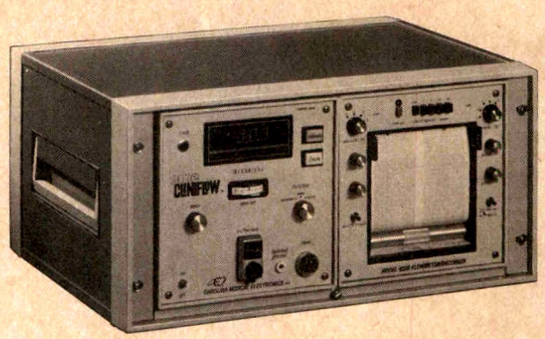
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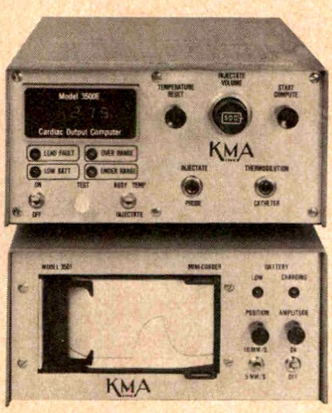




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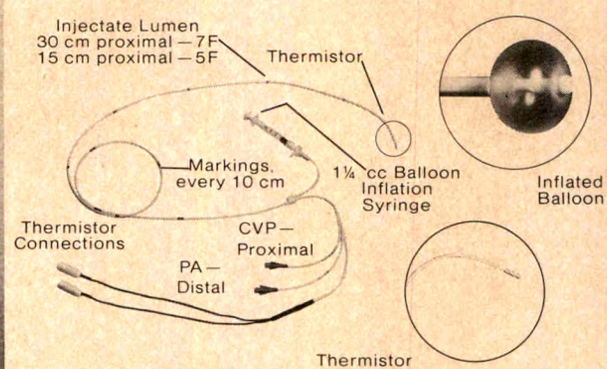
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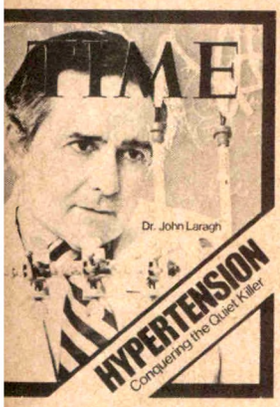
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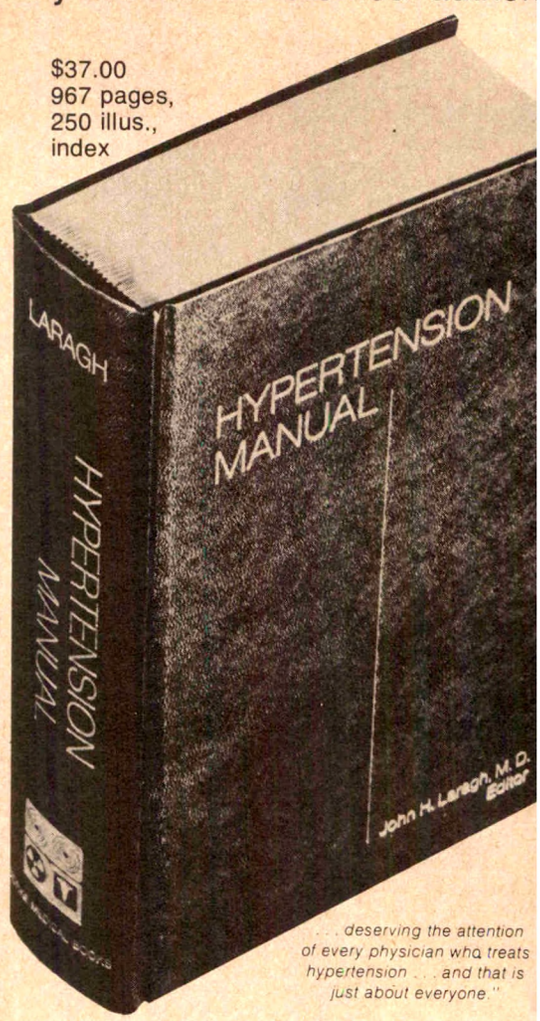


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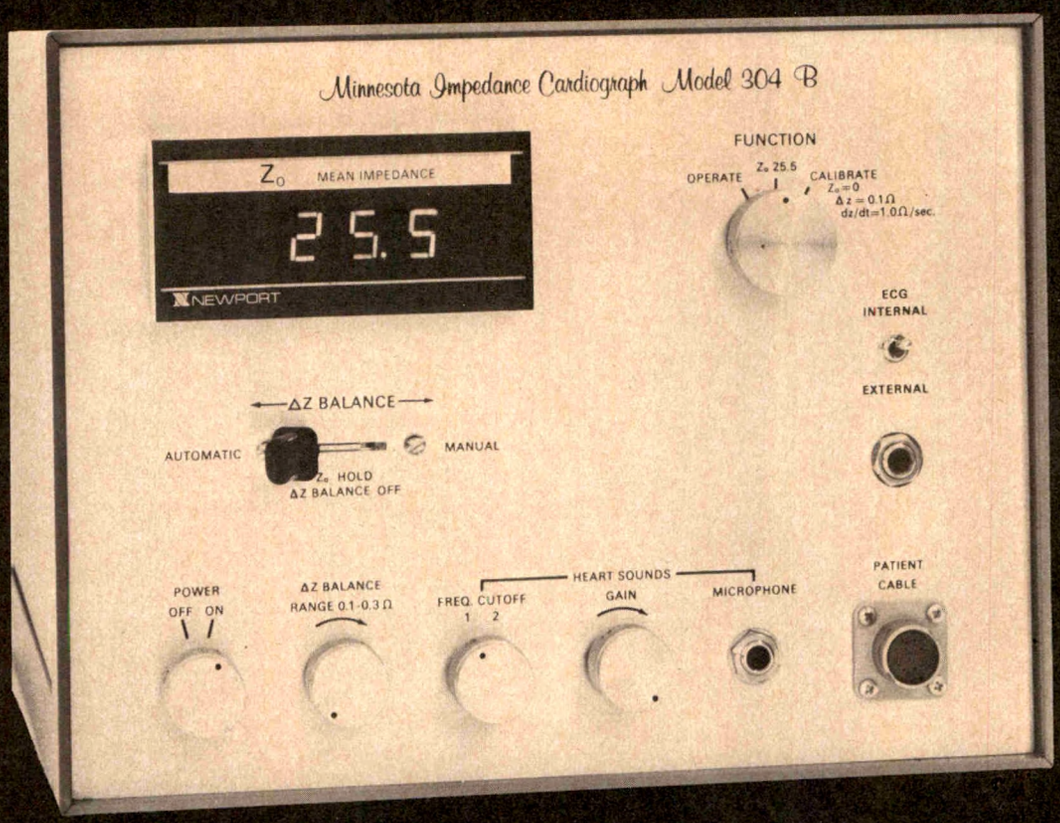
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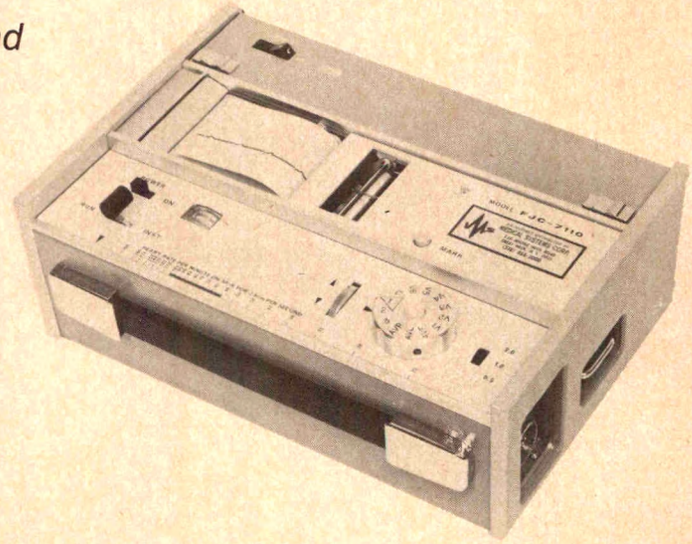
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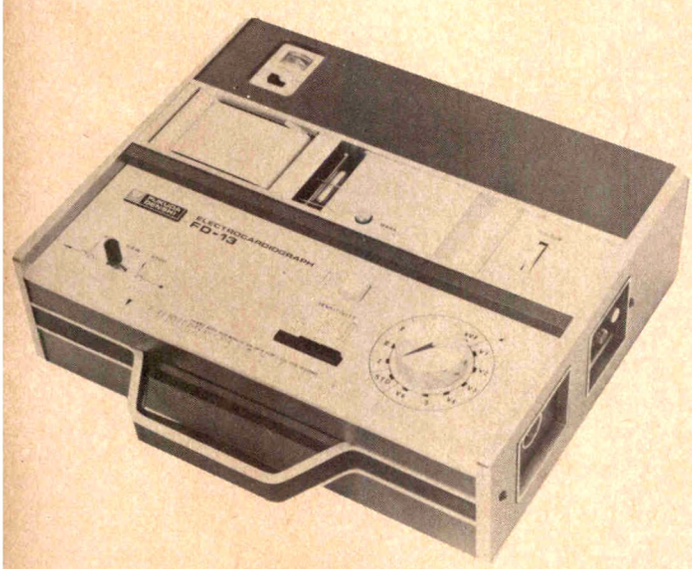
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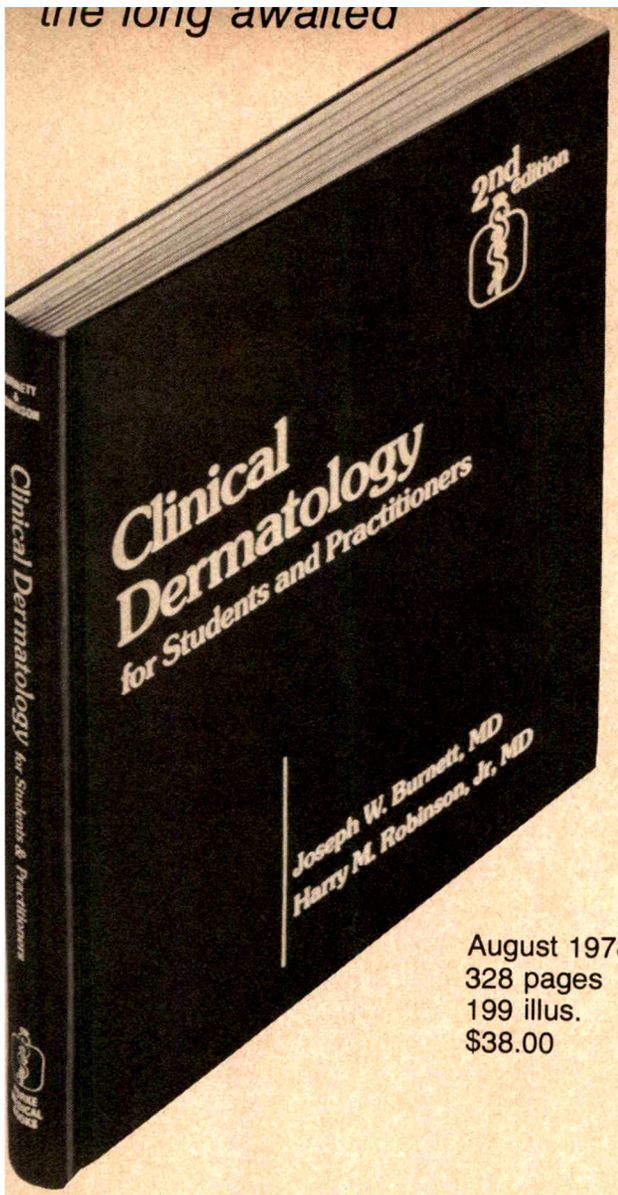
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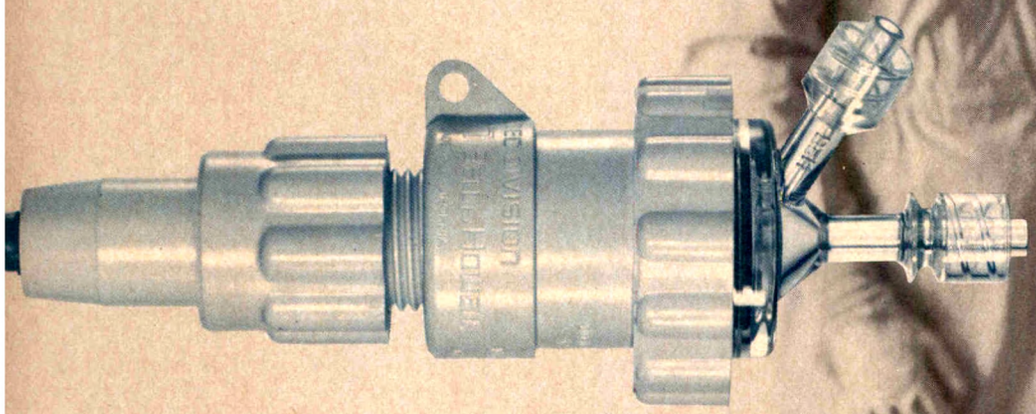
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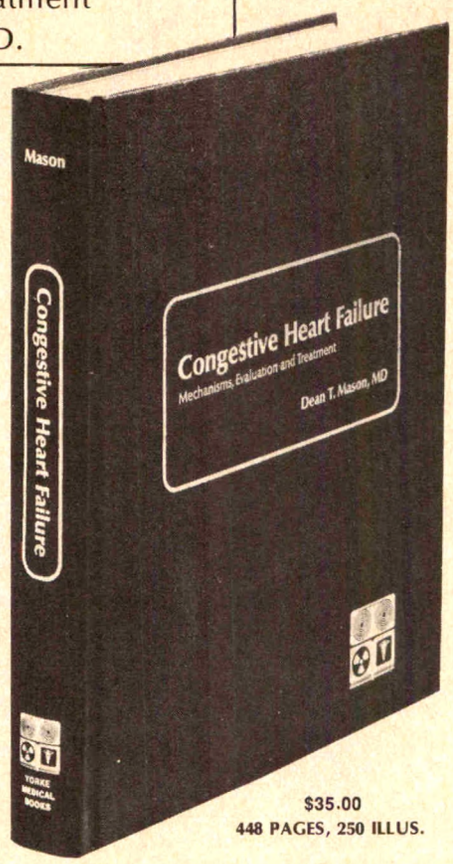
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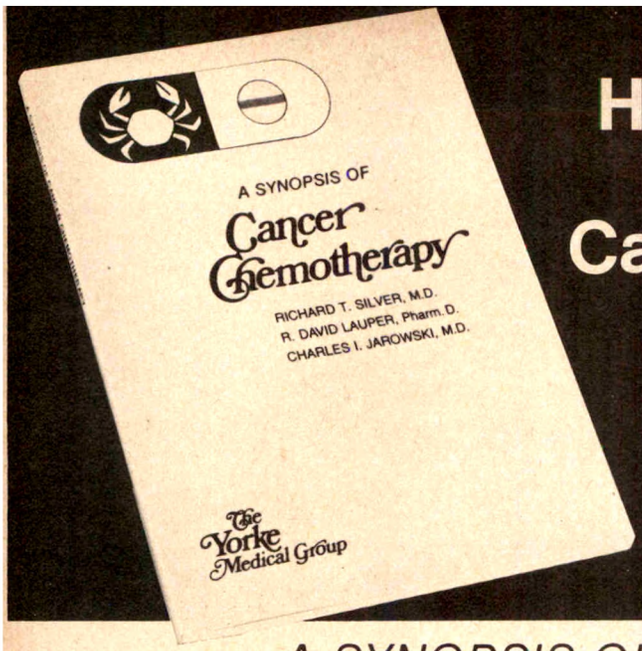
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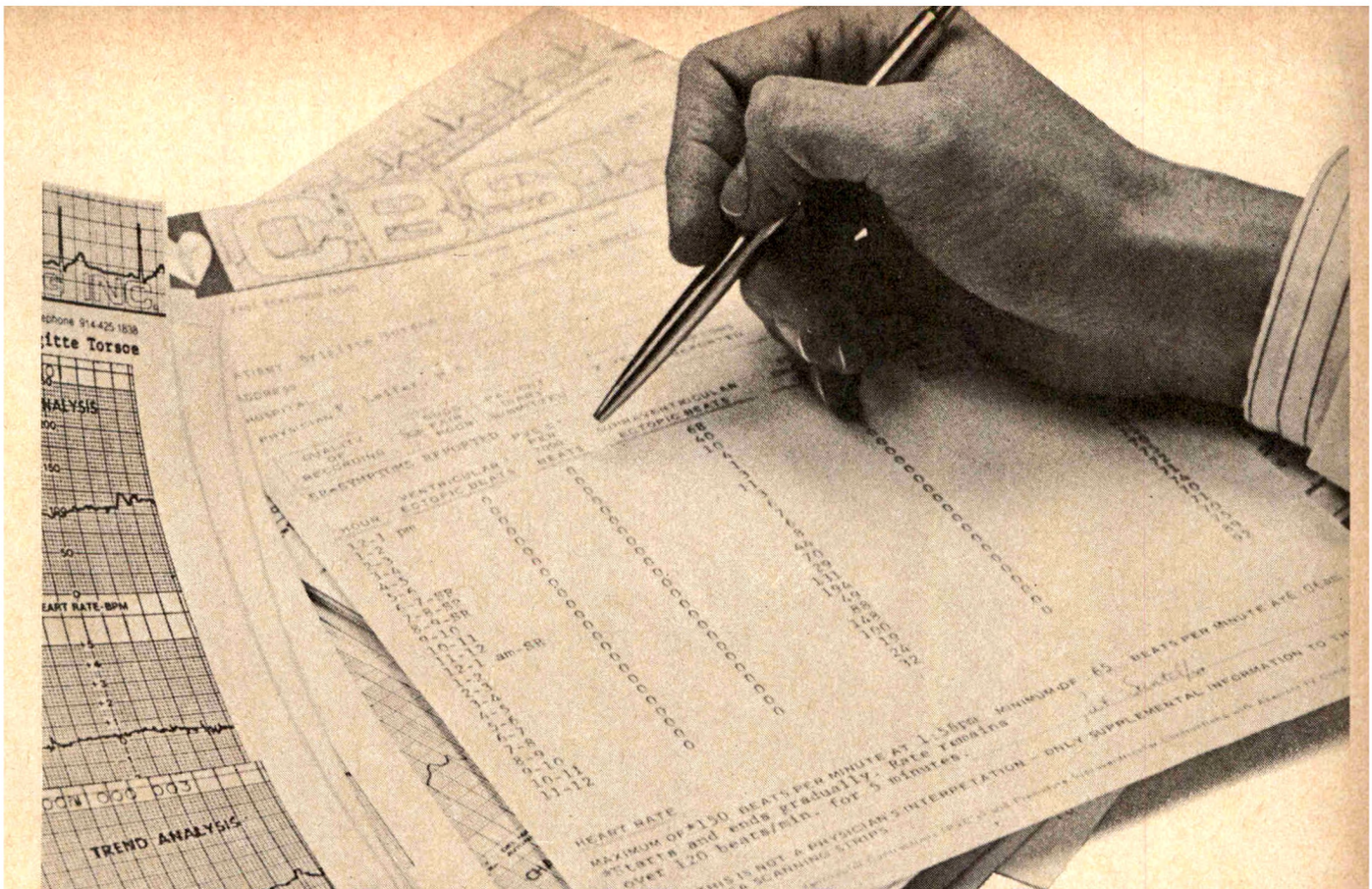
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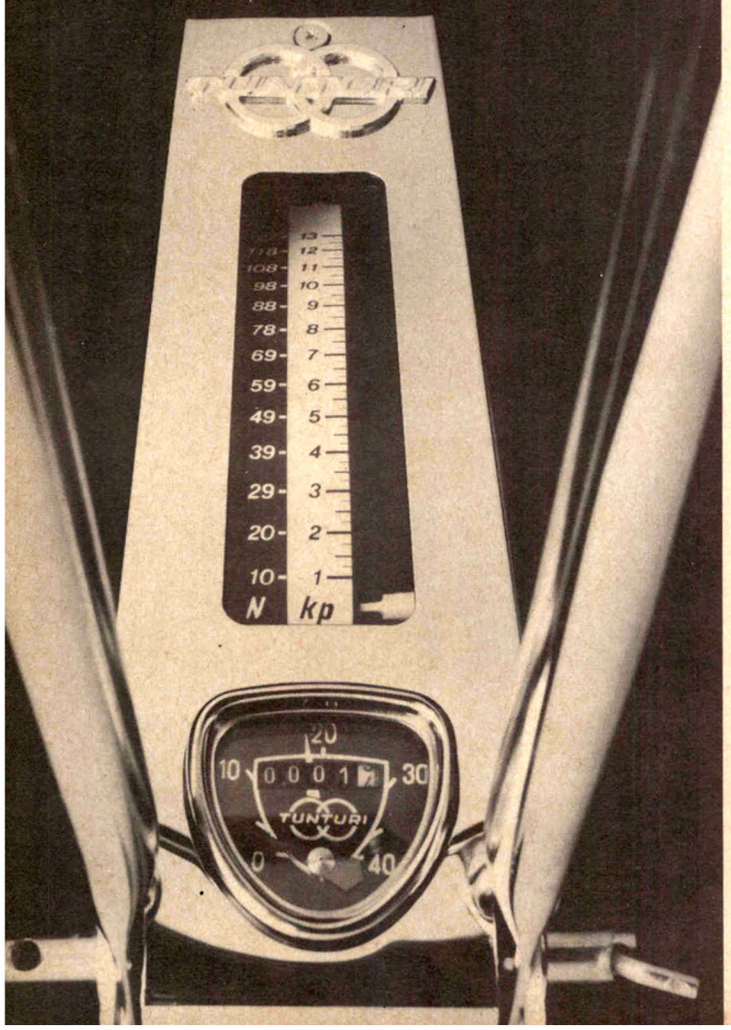
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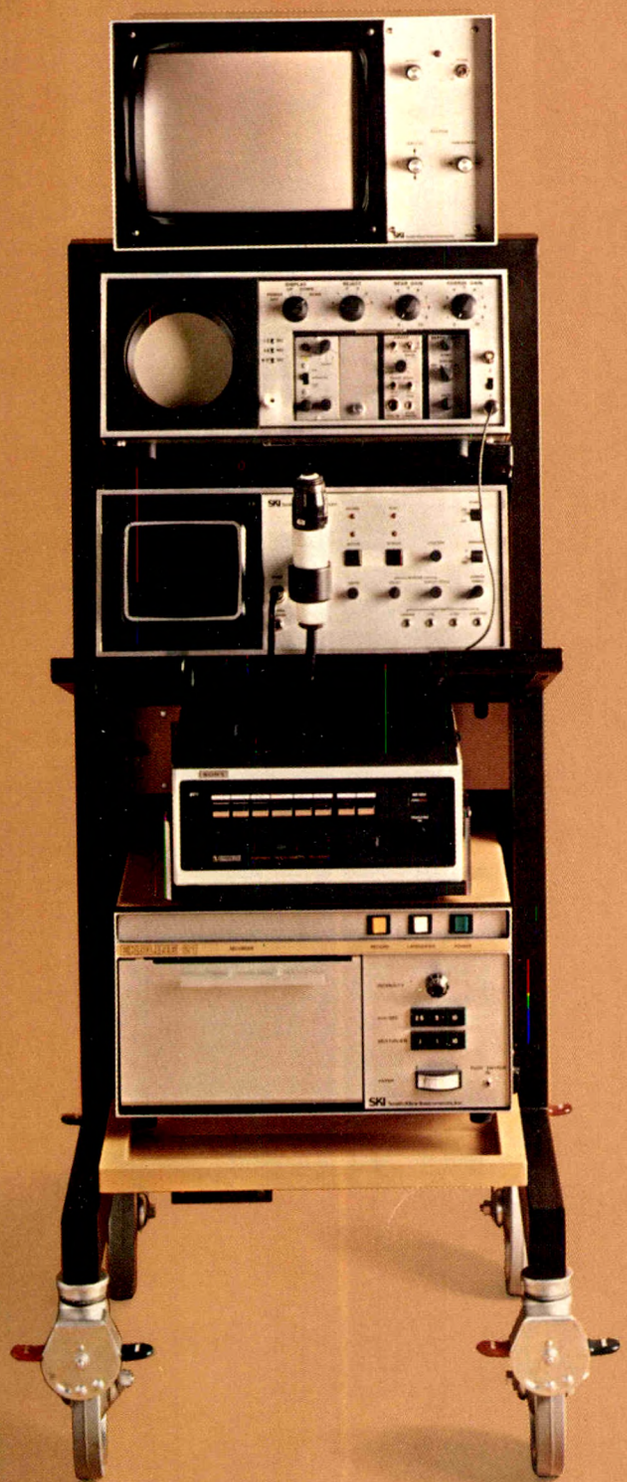
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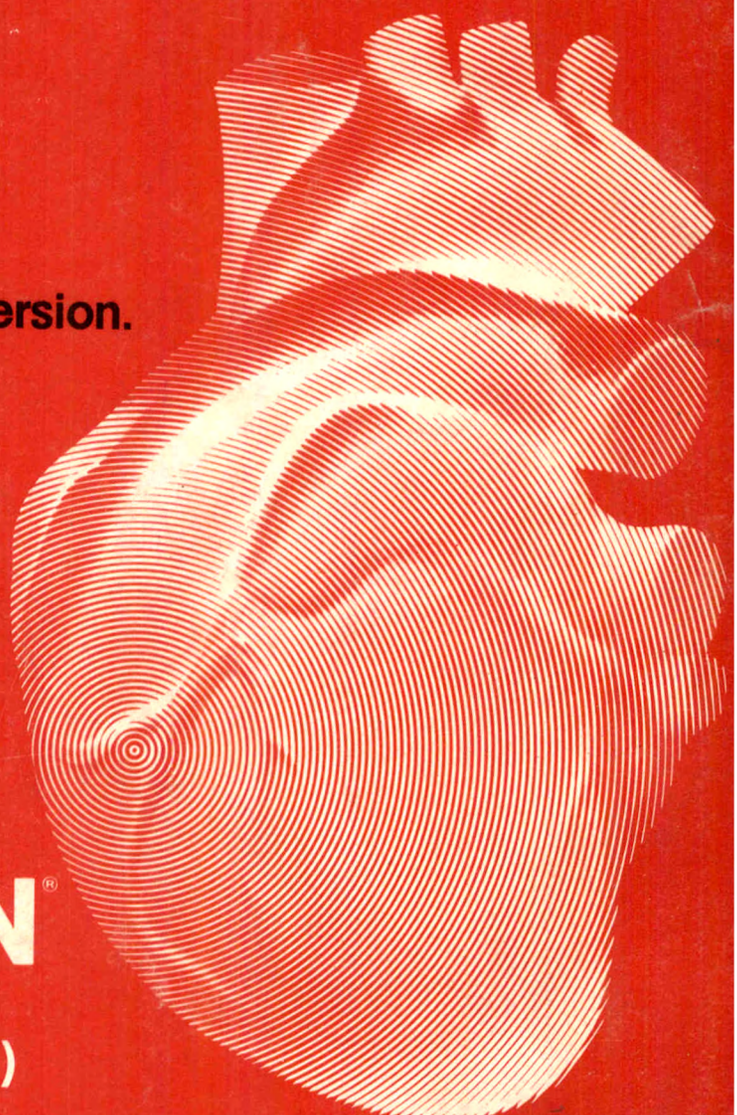
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therapy than a thiazide...



Therapeutic limitations

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, please see the brief summary of prescribing information.

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Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information.

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DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

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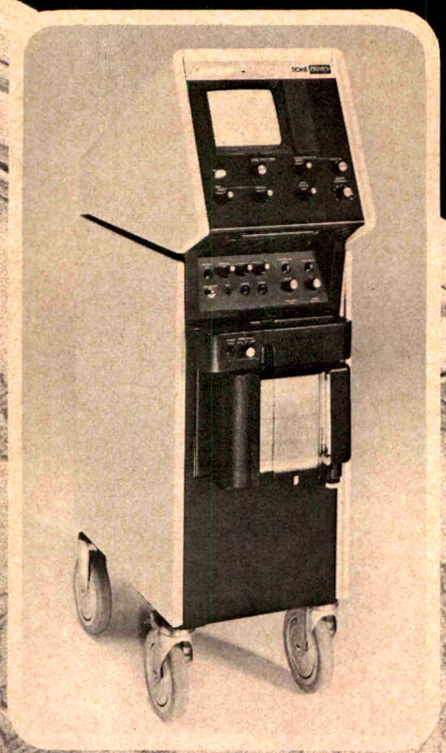
- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- if effective control of blood pressure cannot be maintained on 2.0 g methyldopa daily and a thiazide is not already part of the regimen, a thiazide should be added
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

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Second class postage paid at New York, NY and additional mailing offices. Printed in U. S. A. Trademark® in U. S. Patent Office.

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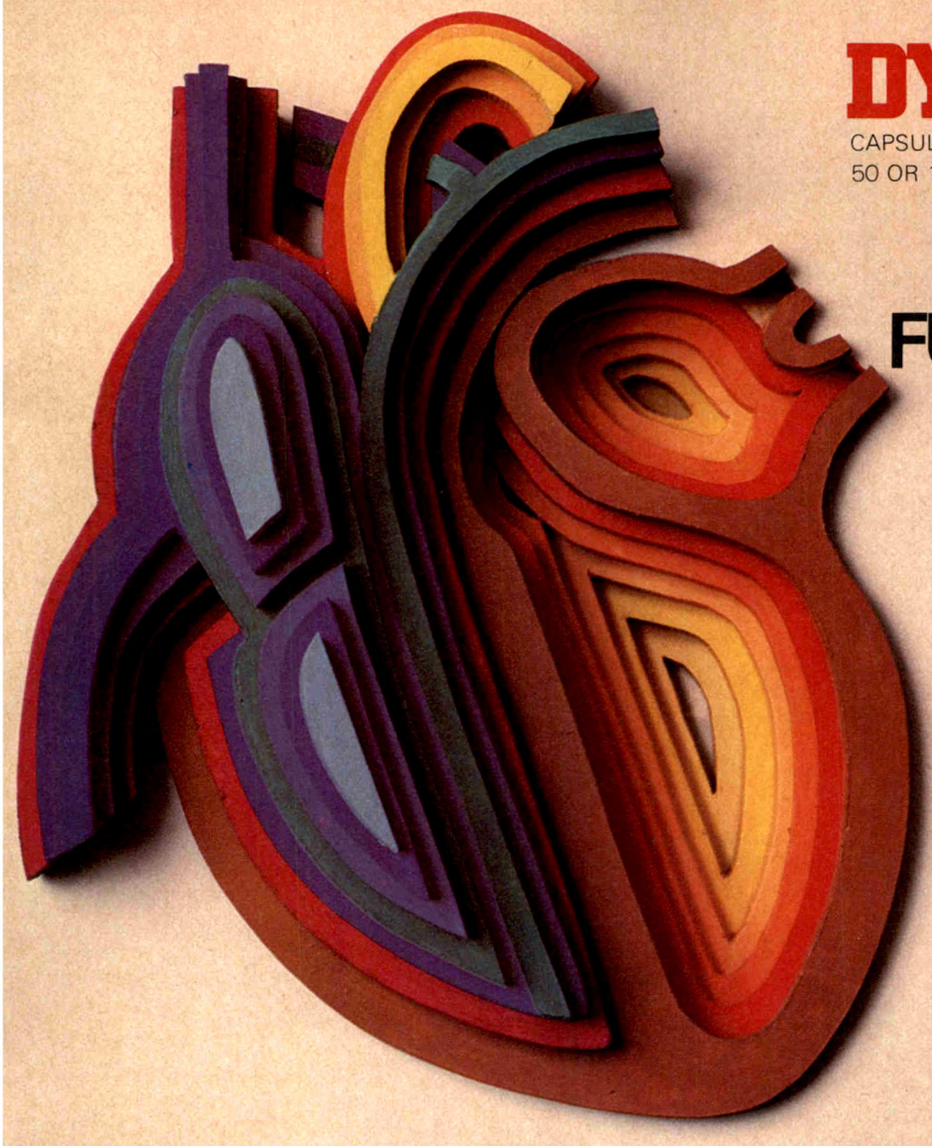
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Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing. 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

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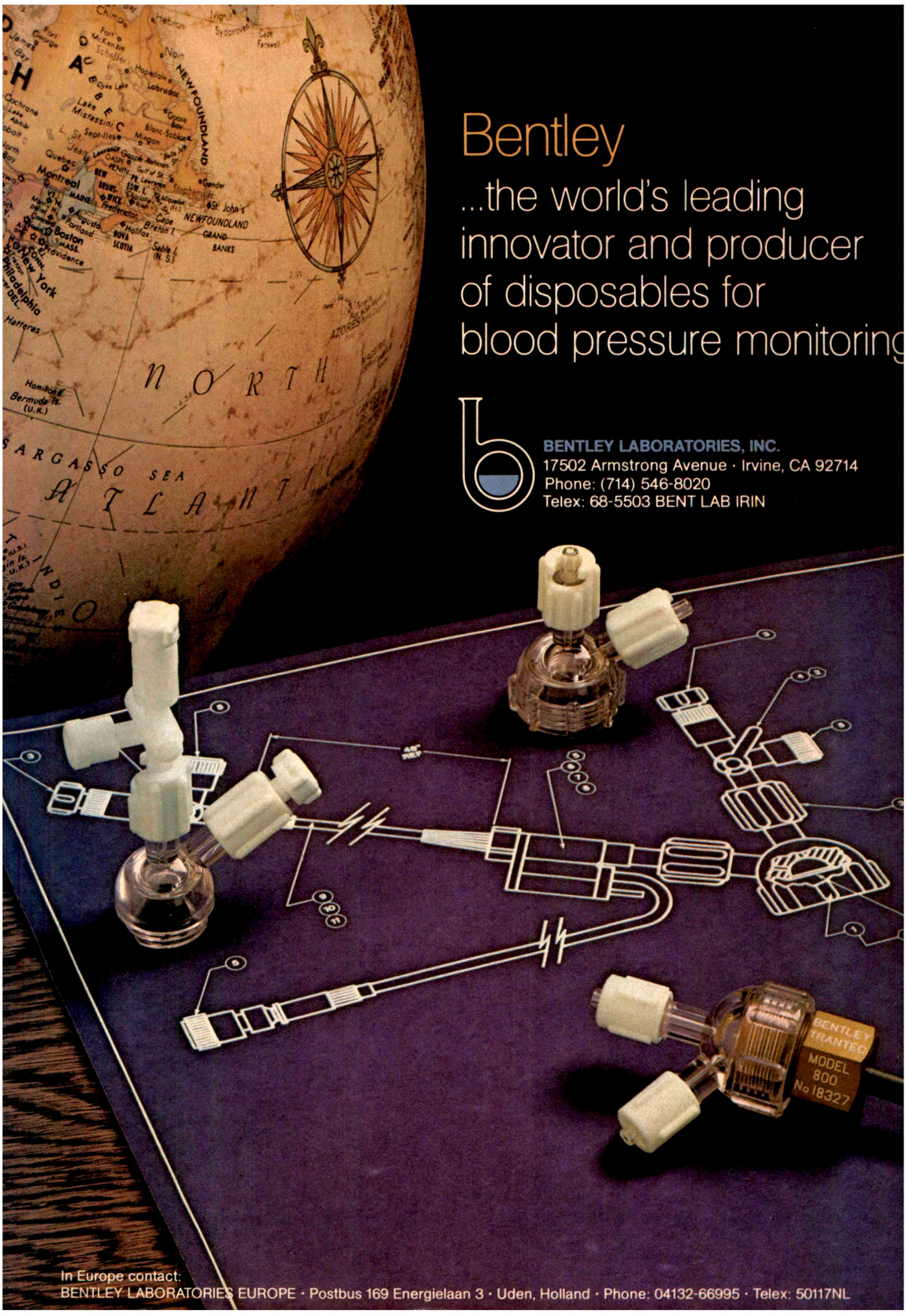
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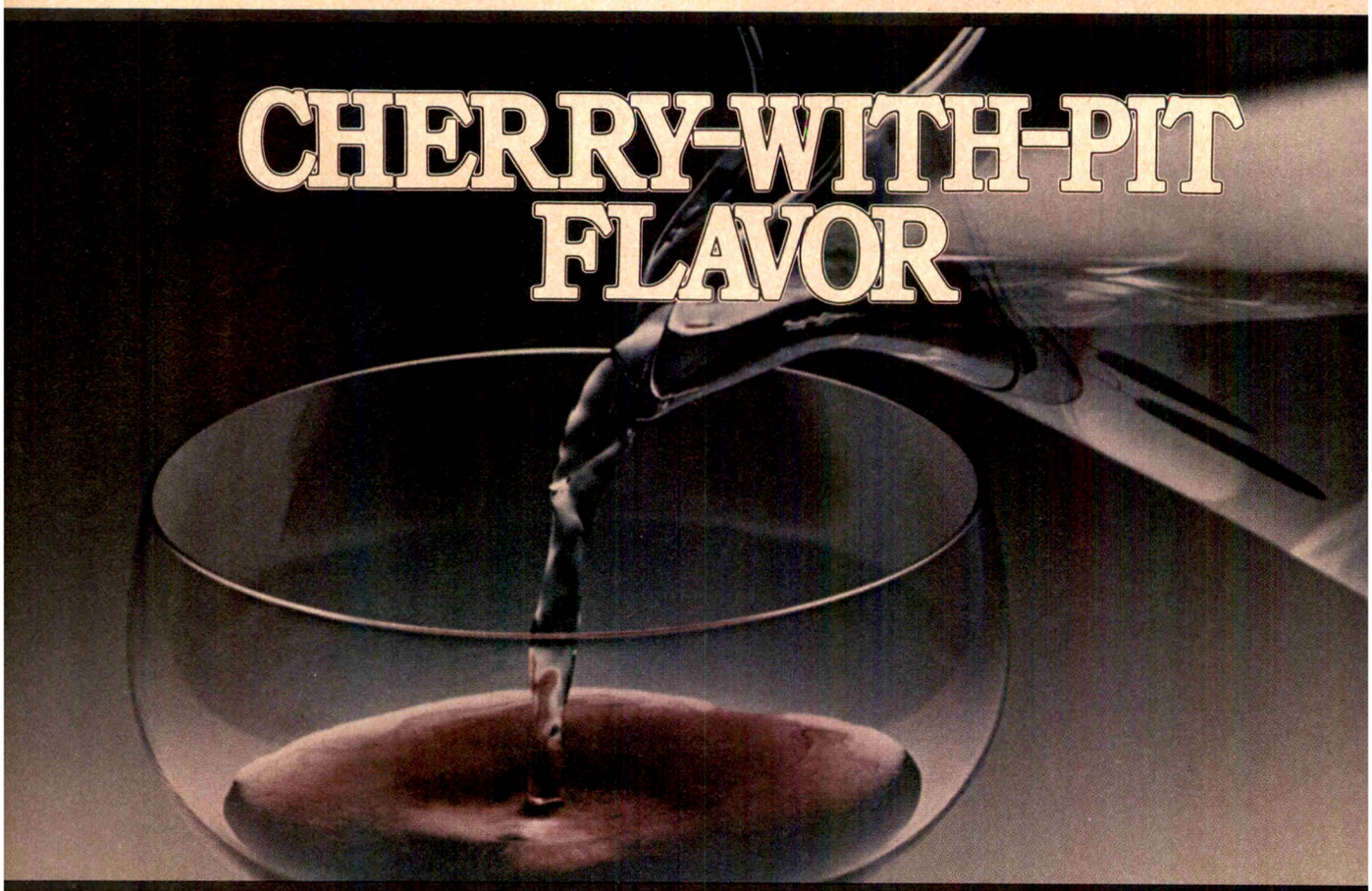
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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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CLINICAL STUDIES

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GERALD M. LAWRIE, GEORGE C. MORRIS, Jr., JIMMY F. HOWELL, TOMAS D. TREDICI and DON W. CHAPMAN

Careful evaluation and follow-up of 1,144 consecutive patients 60 to 76 months after their coronary bypass surgery showed that patients with single, double or triple vessel disease or left main coronary artery disease who had reasonably good preoperative left ventricular function had normal rates of survival more than 5 years after operation in relation to the general U.S. population. Survival was decreased in all patients with poor left ventricular function, in part because of a significant operative mortality. After coronary bypass surgery, the principal determinant of survival beyond 5 years was the preoperative status of left ventricular function, not the number of vessels diseased. The number of diseased vessels preoperatively influenced only perioperative mortality, not late survival. With poor ventricular function, survival is impaired but still superior to that reported with medical treatment only.

716 **Relation of Graded Exercise Test Findings After Myocardial Infarction to Extent of Coronary Artery Disease and Left Ventricular Dysfunction**

THOMAS D. PAINE, LARRY E. DYE, DAVID I. ROITMAN, L. THOMAS SHEFFIELD, CHARLES E. RACKLEY, RICHARD O. RUSSELL, Jr. and WILLIAM J. ROGERS

In 100 consecutive patients graded exercise testing and coronary and left ventricular angiography were safely performed without complication at a median of 4 months after myocardial infarction. An electrocardiographically positive exercise test after infarction was highly predictive (87 percent) of multivessel disease. Such positive tests also identified patients with jeopardized myocardium—normally contracting or hypokinetic myocardium in the zone of distribution of a coronary artery with 70 percent or greater stenosis. S-T elevation during exercise was associated with a large zone of left ventricular asynergy. The categorization of the graded exercise test responses as negative, positive and inconclusive allows a relatively accurate prediction of the extent of coronary artery disease and the degree of left ventricular dysfunction in certain patient subgroups.

724 **Correlation of Electrocardiographic and Pathologic Findings in Healed Myocardial Infarction**

WILLIAM SULLIVAN, ZEEV VLODAVER, NAIP TUNA, LINDA LONG and JESSE E. EDWARDS

Correlating the anatomic and electrocardiographic data in 50 cases of healed myocardial infarction, these investigators conclude that electrocardiographic recognition of myocardial infarction is reasonably good, but the electrocardiogram underestimates the extent of myocardial infarction. The simplified electrocardiographic classification of myocardial infarct site (anteroseptal, inferior and anterolateral) used in this study is preferable to other more detailed classifications and more accurate. Multiple sites of healed infarction were common, but often only one of the sites was recognized electrocardiographically.

Continued on page A15

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and

ing therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three

hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.
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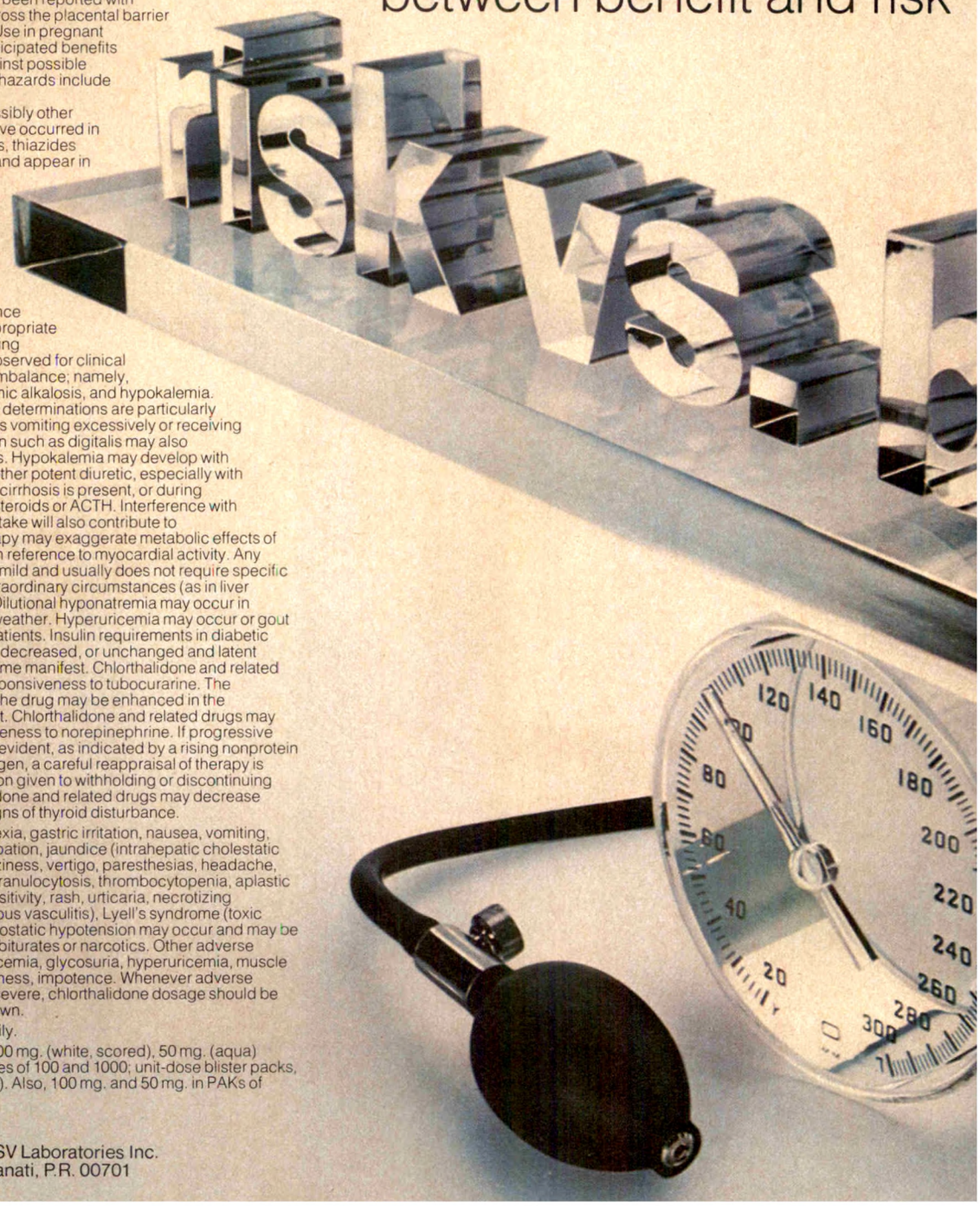
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Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

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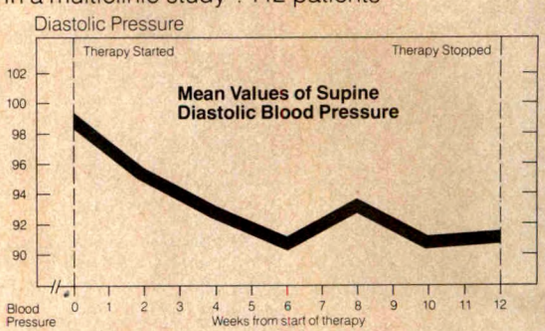
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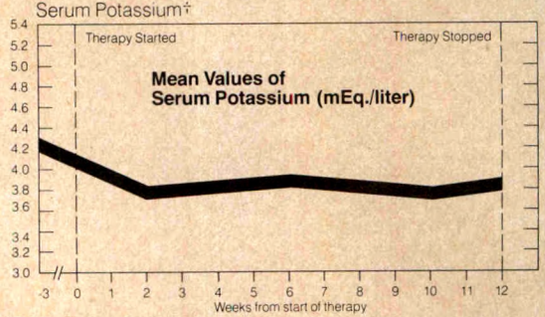
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In a multiclinic study*: 112 patients

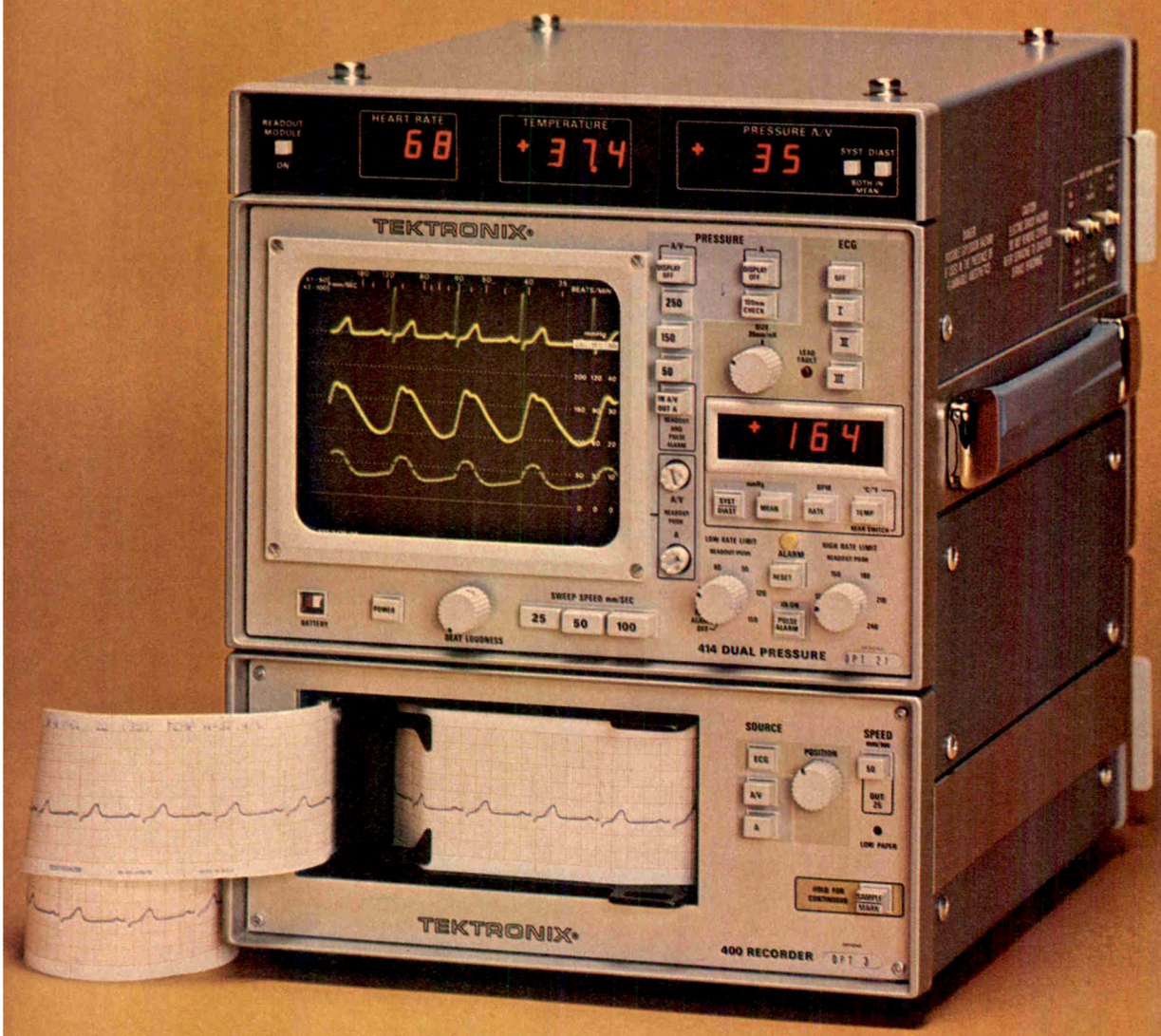






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CONTENTS

733 Apex Sector Echocardiography in Evaluation of the Right Atrium in Patients With Mitral Stenosis and Atrial Septal Defect

FREDERICK G. KUSHNER, WILFRED LAM and JOEL MORGANROTH

These apex sector echocardiographic studies in 20 patients with mitral stenosis, 5 patients with an atrial septal defect and 10 patients without heart disease indicate that this technique may be more sensitive than M mode echocardiography in detecting early right heart involvement in specific cardiac conditions. Left atrial dimension was larger on apex sector echocardiography than on M mode echocardiography in all patients with mitral stenosis. All 11 patients with mitral stenosis who had undergone cardiac catheterization had an elevated mean pulmonary arterial pressure (mean 42 ± 14 mm), and 10 of the 11 had an enlarged right atrium on apex sector echocardiography. The detection of an enlarged right atrium on apex sector echocardiography may be an earlier echocardiographic marker for right heart abnormalities than right ventricular dimension on M mode echocardiography, especially in conditions associated with right ventricular pressure overload.

738 Effect of Catheter Position on the Initiation of Atrial Echoes With Atrial Pacing and Premature Stimulation in Patients With Accessory Pathways

EDWARD L. C. PRITCHETT, DAVID G. BENDITT, WILLIAM M. SMITH and JOHN J. GALLAGHER

This study of 11 patients with an accessory pathway and reciprocating tachycardia confirms the importance of catheter position as a variable in the initiation of atrial echoes in patients with accessory pathways. Failure to induce tachycardia with atrial extrastimuli in patients with a history of palpitations may be related to choice of stimulation site. If no tachycardia is induced with extrastimuli using one atrial site, then a second site (preferably in the opposite atrium) should be tested. This study further shows that the echo zone is profoundly influenced by stimulation site and that any patient may have several echo zones. The merit of serial studies as a clinical tool can be evaluated only if the position of the catheter is well controlled.

746 Stress Myocardial Imaging in Mitral Leaflet Prolapse Syndrome

GEORGE J. KLEIN, WILLIAM J. KOSTUK, DEREK R. BOUGHNER and MICHAEL J. CHAMBERLAIN

This study of 32 patients found stress myocardial imaging to be a helpful noninvasive technique for differentiating patients with mitral leaflet prolapse syndrome from those with mitral leaflet prolapse associated with coronary artery disease. All patients with this syndrome and normal coronary arteries on arteriography had normal stress myocardial scans indicating that regional myocardial perfusion, as demonstrated with this technique, was normal on exercise. In contrast, 9 of the 10 subjects with significant coronary artery disease and prolapse had perfusion defects on exercise. The presence of normal myocardial perfusion at rest and during exercise in patients with mitral leaflet prolapse alone but not in patients with associated coronary artery disease creates doubt concerning the ischemic origin of chest pain in this syndrome.

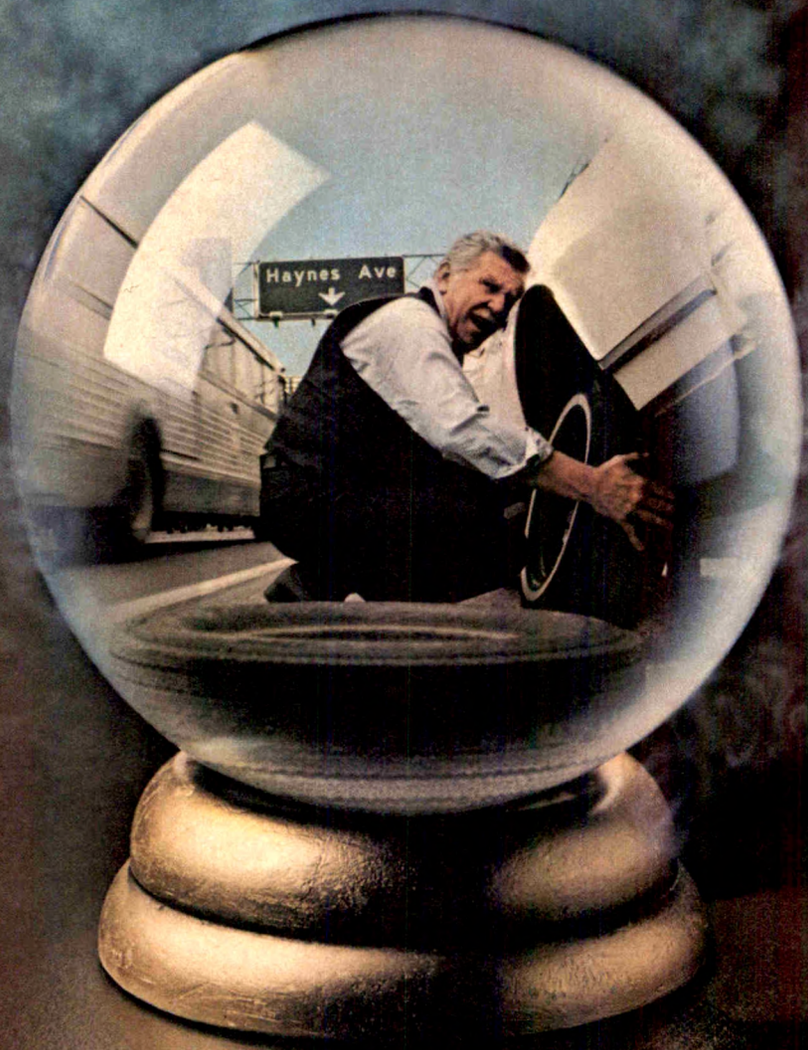
751 Noninvasive Assessment of Coronary Stenoses by Myocardial Imaging During Pharmacologic Coronary Vasodilatation. III. Clinical Trial

PETER C. ALBRO, K. LANCE GOULD, R. JEFFREY WESTCOTT, GLEN W. HAMILTON, JAMES L. RITCHIE and DAVID L. WILLIAMS

Comparing the clinical diagnostic sensitivity and specificity of thallium myocardial imaging after coronary vasodilatation induced by intravenous dipyridamole with those of thallium imaging after treadmill exercise stress in 62 patients, these investigators found that pharmacologic coronary vasodilatation is as effective as maximal treadmill exercise in creating myocardial perfusion abnormalities detectable with thallium-201 imaging in man. Angina and S-T depression occurred more frequently with exercise than with dipyridamole. The infusion of dipyridamole appears particularly useful in patients who are unable or unwilling to undergo maximal exercise testing. The major disadvantage is the absence of additional diagnostic information provided by the S-T segment response during exercise.

Continued on page A17

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EXPERIMENTAL STUDIES

761 **Assessment of Coronary Stenoses With Myocardial Perfusion Imaging During Pharmacologic Coronary Vasodilatation. IV. Limits of Detection of Stenosis With Idealized Experimental Cross-Sectional Myocardial Imaging**

K. LANCE GOULD

These 12 open chest dog studies demonstrate the validity of a technique for detecting 40 percent diameter stenosis of coronary arteries using cross-sectional myocardial imaging of regional and epicardial-endocardial perfusion during maximal pharmacologic coronary vasodilatation. Requirements for a noninvasive imaging technique sensitive enough to identify mild coronary lesions for diagnostic screening purposes in humans and animals are detailed. However, it remains to be determined whether sensitivity comparable with these experimental results can be achieved with noninvasive techniques in vivo.

769 **Effect of Propranolol and Nitroglycerin Plus Methoxamine on Transmural Creatine Kinase Activity After Acute Coronary Occlusion**

GARY J. JESMOK, GARRETT J. GROSS and HAROLD F. HARDMAN

After acute occlusion of the left anterior descending coronary artery in 27 open chest anesthetized dogs, nitroglycerin plus methoxamine, unlike propranolol, significantly decreased subendocardial creatine kinase depletion after 5 hours of occlusion. These findings demonstrate the unique ability of both drugs together to protect the subendocardium during ischemic insult. The transmural creatine kinase values show the subendocardium is subject to greater ischemic injury than the subepicardium, partly a result of the maldistribution of blood flow that occurs after coronary occlusion. Furthermore, oxygen consumption in the subendocardium exceeds that in the subepicardium. Propranolol, a drug shown to diminish myocardial necrosis, did not affect the extent of ischemic subendocardial creatine kinase depletion after 5 hours of coronary occlusion. It appears that propranolol is not capable of protecting the ischemic subendocardium from necrosis after 5 hours of coronary occlusion. The beneficial effects of nitroglycerin and methoxamine may involve several effects of the drugs on the multiple determinants of myocardial oxygen supply and demand.

774 **Origin of So-Called Right and Left Ventricular Arrhythmias in Acute Myocardial Ischemia**

ELIESER KAPLINSKY, SATOSHI OGAWA, JAMES KMETZO and LEONARD S. DREIFUS

Attempting to distinguish between "benign" and "malignant" ventricular premature complexes on the basis of their anatomic origin, these investigators studied the origin of ventricular arrhythmias associated with acute myocardial ischemia in 32 dogs after ligation of the left anterior descending coronary artery. So-called left and right ventricular arrhythmias were associated with a similar delay and fragmentation of the left ventricular ischemic epicardial activity. Multiple exit points in the right and left ventricles increased before ventricular fibrillation occurred. This study supports clinical observations that ventricular premature complexes and ventricular tachycardia exiting from the right ventricle may be the result of myocardial injury in the left ventricle. Acute injury to the anteroseptal region of the heart resulted in arrhythmias exiting in both ventricles. The apparent site of origin of ventricular arhythmias should not be the sole determinant of the benign or malignant properties of the arrhythmia.

781 **Effect of Stenotic Dimensions and Blood Flow on the Hemodynamic Significance of Model Coronary Arterial Stenoses**

KIRK LIPSCOMB and STEVEN HOOTEN

These results confirm that the hemodynamic significance of coronary stenoses can be estimated with the use of theoretically sound concepts and model coronary arterial stenoses. However, greater accuracy in the measurement of dimensions and flow would improve the precision of this approach. In these studies the length of a stenosis exerted small effects on the pressure gradient due to turbulent flow. Varying the exit angle of the stenosis from 10° to 20° did not affect the gradient. The ratio of gradient due to turbulent flow to gradient due to nonturbulent flow ratio increases as flow increases. The relative significance of changes in length of the stenosis and blood viscosity and flow depends on the flow rate. The three most important determinants of the pressure gradient across a stenosis are, in descending order of importance, the diameter of the stenosis, the flow through it and the length of the stenosis.

Continued on page A19

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PEDIATRIC CARDIOLOGY

793 Idiopathic Hypertrophic Subaortic Stenosis in the Young

GARRICK I. FIDDLER, ABDUL J. TAJIK, WILLIAM H. WEIDMAN, DWIGHT C. McGOON, DONALD G. RITTER and EMILIO R. GIULIANI

The high mortality among untreated patients (7 of 13) in this study of 36 young subjects with idiopathic hypertrophic subaortic stenosis strongly suggests that all patients with this disorder should receive some form of treatment, preferably propranolol or surgery. However, neither guarantees protection against sudden death, so common in this disorder. Surgical intervention, offering symptomatic improvement in most cases over a long-term follow-up period, is especially recommended in patients who present with severe left ventricular outflow obstruction (basal pressure gradient of 80 mm Hg or more) with or without symptoms and in those who have angina, dyspnea or syncope while taking propranolol in adequate doses. Twelve of the 16 surgical patients survived and had good relief of symptoms. Echocardiograms proved a useful noninvasive diagnostic clinical aid. The presence of an asymmetrically thickened hypocontractile septum and systolic anterior motion of the mitral valve was specific for this condition.

800 Truncal or Aortic Valve Stenosis in Functionally Single Arterial Trunk. A Clinical, Hemodynamic and Pathologic Study of Six Cases

RAMAN G. PATEL, ROBERT M. FREEDOM, KENNETH R. BLOOM and RICHARD D. ROWE

Stenosis of the semilunar valve in the presence of a functionally single arterial trunk is uncommon; data on six patients with this anomaly are reported. Echocardiography was of great help in the initial clinical assessment of these patients and as an adjunct to cardiac catheterization. The presence of semilunar valve stenosis adversely affected the prognosis. Its added burden may further compromise the functional status of the myocardium already jeopardized as a result of hypoxia in pulmonary atresia and left ventricular diastolic overload in truncus arteriosus. Four patients died despite intensive medical or surgical treatment, or both. Clinical recognition of systemic semilunar valve stenosis in infants with a functionally single arterial trunk is important because it may have specific implications in determining initial therapy.

810 Estimation of Pulmonary/Systemic Resistance Ratios From Echocardiographic Systolic Time Intervals in Young Patients With Congenital or Acquired Heart Disease

ERIC W. SPOONER, BURTON L. PERRY, AARON M. STERN and JOAN M. SIGMANN

This study comparing the right ventricular preejection period/ejection time (RPEP/RVET) ratio with left ventricular preejection period/ejection time ratio (LVEP/LVET) in 25 patients undergoing cardiac catheterization found a strong correlation between the ratio (RPEP/RVET)/(LPEP/LVET) = R/L and the ratio of pulmonary arteriolar resistance/systemic arteriolar resistance (PAR/RS), especially when R/L was correlated with $\log_{10}$ PAR/RS ($r = 0.902$). The use of regression equations, as described in this report, should allow a rough estimation of pulmonary arteriolar resistance/systemic arteriolar resistance ratio and prove useful to clinicians in the timing or avoidance of cardiac catheterization with its attendant risk and expense.

REPORTS ON THERAPY

817 Isoproterenol As a Potential Pulmonary Vasodilator in Primary Pulmonary Hypertension

FUHEID S. DAOUD, JOHN T. REEVES and DENNIS B. KELLY

This systematic study of the responses to various pharmacologic agents in six patients with pulmonary hypertension suggests that hypoxia, histamine and prostaglandin do not play a role in the etiology of the condition but that the role of an immune mechanism deserves further investigation. After the acute intravenous administration of

Continued on page A21


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the potent pulmonary vasodilator drug isoproterenol, vascular resistance decreased in five of the six subjects. The sublingual administration of isoproterenol significantly decreased vascular resistance in one of four patients studied. This patient has been on maintenance doses for 30 months. These data indicate that isoproterenol may be useful in some patients with primary pulmonary hypertension.

823 Effect of Afterload Reduction on Plasma Volume During Acute Heart Failure

ROBERT J. HENNING and MAX HARRY WEIL

These data in 14 men and women (median age 69) with arteriosclerotic heart disease and acute cardiogenic pulmonary edema suggest that acute congestive heart failure with pulmonary edema, unlike chronic congestive heart failure, is assocciated with extravasation of large quantities of plasma water from the intravascular compartment into the interstitial compartment and contraction of the intravascular plasma volume. Treatment with the alpha adrenergic blocking agent phentolamine to reduce afterload facilitated return of hypo-oncotic fluid from the interstitial compartment back into the intravascular compartment with expansion of plasma volume and reduction of colloid osmotic pressure and hemoglobin concentration. After the administration of phentolamine, left ventricular filling pressure, pulmonary arterial wedge pressure and pulmonary capillary pressure decreased, and cardiac index increased. In addition, there is evidence that furosemide, also used in these patients, may act as a vasoactive agent, independent of its renal effects, and may be potentially useful for interrupting the vicious cycle of cardiac failure, increased afterload and volume depletion. The treatment of acute heart failure with improvement in ventricular function after vasodilator therapy appears associated with expansion of the plasma volume.

REVIEWS

828 Spectrum of Regular Tachycardias With Wide QRS Complexes in Patients With Accessory Atrioventricular Pathways

DAVID G. BENDITT, EDWARD L. C. PRITCHETT and JOHN J. GALLAGHER

Twenty-six patients (15 percent) manifested a regular tachycardia with a wide QRS complex suggesting ventricular excitation in this study of 163 patients with accessory atrioventricular pathways. In this group atrial flutter with 1:1 anterograde conduction over an accessory pathway (58 percent) and antidromic reciprocating tachycardia (27 percent) were the most frequently observed arrhythmias resulting in regular wide QRS tachycardias. Ventricular tachycardia was proved in only one patient. The definitive diagnosis of an arrhythmia during these tachycardias is often complex and usually requires careful study using intracardiac electrode catheter techniques. The frequency and clinical significance of these tachycardias can be assessed adequately only with the use of ambulatory electrocardiographic monitoring.

SPECIAL REPORT

839 Unstable Angina Pectoris: National Cooperative Study Group to Compare Surgical and Medical Therapy. II. In-Hospital Experience and Initial Follow-Up Results in Patients With One, Two and Three Vessel Disease

NATIONAL COOPERATIVE STUDY GROUP

This prospective randomized study of 288 patients with unstable angina pectoris less than age 70 years showed a hospital mortality rate of 5 percent in patients treated surgically and 3 percent in patients treated medically (difference not significant). In the first year after hospital discharge, class III or IV angina was more common in medically than in surgically treated patients. During an average follow-up period of 30 months, 36 percent of the medically treated patients later underwent surgery to relieve unacceptable angina. These results indicate that patients with unstable angina pectoris can be managed acutely with intensive medical therapy, including propranolol and long-acting nitrates, with adequate control of pain in most patients and no increase in early mortality or myocardial infarction rates. If the patient's angina fails to respond to intensive medical therapy, further elective surgery can be performed later with a low risk and good clinical results.

Continued on page A23



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HISTORICAL MILESTONES

849 Centenary of the First Correct Antemortem Diagnosis of Coronary Thrombosis by Adam Hammer (1818–1878): English Translation of the Original Report

J. T. LIE

This historical milestone directs attention to the first antemortem clinical diagnosis (confirmed at autopsy) of coronary thrombosis reported by Dr. Adam Hammer in 1878.

DIAGNOSTIC SHELF

853 Cross-Sectional Echocardiographic Diagnosis of Large Left Atrial Tumor and Extracardiac Tumor Compressing the Left Atrium. Limitation of M Mode Echocardiography in Distinguishing the Two Lesions

JUNICHI YOSHIKAWA, IRFAN SABAH, KOJI YANAGIHARA, TAKANE OWAKI, HIROSHI KATO and KIICHIRO TANEMOTO

This paper reports the occurrence of an M mode echocardiographic pattern mimicking a left atrial tumor in patients with extracardiac tumors and the greater accuracy of cross-sectional echocardiography in distinguishing between a large left atrial tumor and an extracardiac tumor compressing the left atrium. Cross-sectional echocardiography allowed direct visualization of the location, size and movement of the tumor in all three cases. This technique appears indicated in all patients with suspected mediastinal or esophageal tumors to permit earlier and more frequent detection of tumors causing left atrial obstruction.

858 Hemodynamic Pattern Resembling Pericardial Constriction After Acute Inferior Myocardial Infarction With Right Ventricular Infarction

DOUGLAS P. JENSEN, JAMES P. GOOLSBY, Jr. and PHILIP B. OLIVA

Cardiac catheterization in two patients with acute inferior myocardial infarction complicated by cardiogenic shock revealed right coronary occlusion proximal to the right ventricular marginal branches and a hemodynamic pattern resembling constrictive pericarditis. This pattern resolved in one survivor at repeat catheterization 7 weeks after infarction. The mechanism for constructive hemodynamics in these patients is unclear. The prognosis is better than that of cardiogenic shock after anterior myocardial infarction. Recognition of this syndrome is important because fluid therapy, with or without pharmacologic or mechanical unloading of the left ventricle, may be instrumental in improving cardiac function and survival.

CASE REPORTS

862 Fortuitous Rupture of Aortic Aneurysm: A Catastrophic Event Affording Time for Surgical Cure

JAMES B. YOUNG, JOHN O. F. ROEHM, Jr., GERALD M. LAWRIE, GEORGE C. MORRIS, Jr., GEORGE P. NOON, JIMMY F. HOWELL, RAFAEL ESPADA and RICHARD R. MILLER

These three case reports illustrate the fortuitous nature of the rupture of an aortic aneurysm into a vascular structure and the diagnostic criteria that afford temporary survival and the opportunity for successful surgical repair. In the first patient an atherosclerotic abdominal aortic aneurysm ruptured into the inferior vena cava; in the second, an aortic-left pulmonary arterial fistula developed as a result of a syphilitic thoracic aortic aneurysm; in the third, a dissecting aneurysm of the aortic root communicated with the right ventricle after coronary bypass surgery. These three cases emphasize the need for early accurate diagnosis and appropriate surgical measures. Two patients survived surgical intervention.

Continued on page A25



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Internal Systolic Time Intervals in Hypertrophic Cardiomyopathy—G. S. Uhl, J. P. Murgo, J. R. Logsdon, et al.

Pacemaker Treatment of Drug-Resistant Atrial Tachycardia—E. R. Arbel

Echocardiographic Estimation of Peak Left Ventricular Pressure in Aortic Stenosis—D. Bennett, K. U. Aziz, A. van Grondelle, et al.

Echocardiographic Patterns of Prosthetic Valve Malfunction—G. Jacovella, P. Giampaolo, G. Gambelli, et al.

Optimal Electrocardiography—G. E. Dower

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r referring Mr. Hoosier to our laboratory to be
a candidate for coronary surgery. Mr. Hoosier was

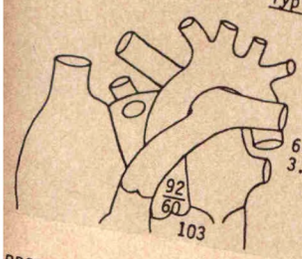
CARDIAC DIAGNOSTIC AFFILIATES

University Community Hospital

CARDIAC CATHETERIZATION REPORT A - Page 2

Name: Harold Hoosier 58, M Record #5542
Date: 7/20/78 Ht: 155cm Wt: 80kg BSA: 1.78m2

Typical Hemodynamics



	Sample Site	Pressure Data Normal	Phasic	Mean	HR	Note
LV	(mid)	140/12	87/1		72	1
LV	OFT	140/12	103/14			
AO	ASP	140/90	92/60	73	78	2

6.93L/min.
3.89L/min/m2

Note 1: Pre-angio with balloon off.
Note 2: Pullback, post-angio with balloon off.

RDIAC DIAGNOSTIC AFFILIATES
iversity Community Hospital
Union Ave., Sudbury, Mass. 01776

Office: 617-443-9969
Hospital: 617-443-9886

CARDIAC CATHETERIZATION REPORT A

Harold Hoosier 58, M Record #5542
7/20/78 Ht: 155cm Wt: 80kg BSA: 1.78m2

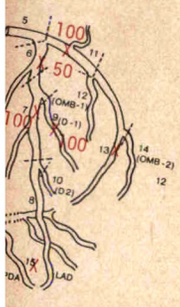
ing physician: John Woden, M.D.
ing physician: Ward Halsom, M.D., Carol S. Perch, M.D.

l diagnosis: Pre-infarction angina / medical failure
ion for study: Evaluate for coronary surgery

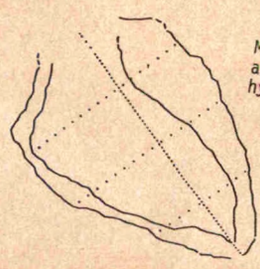
e: Hemodynamics: Left heart, right femoral approach
Angiography: LV, RAO view. Coronaries via Judkins.
Other: Performed during balloon counterpulsation
Complications: None.

: 1. Good LV function, normal valves with mild anterolateral and infero-apical hypokinesis.
2. Severe 3-vessel coronary disease: 99% RCA occlusion, 50% proximal, 100% mid-LAD, 100% first diagonal, 100% proximal left circumflex.
3. Retrograde filling of LAD from proximal RCA and posterior descending, plus collaterals to the circumflex show good distal vessels.

n: Coronary artery bypass graft surgery--immediate standby basis.



aphy



Moderate anterolateral hypokinesis

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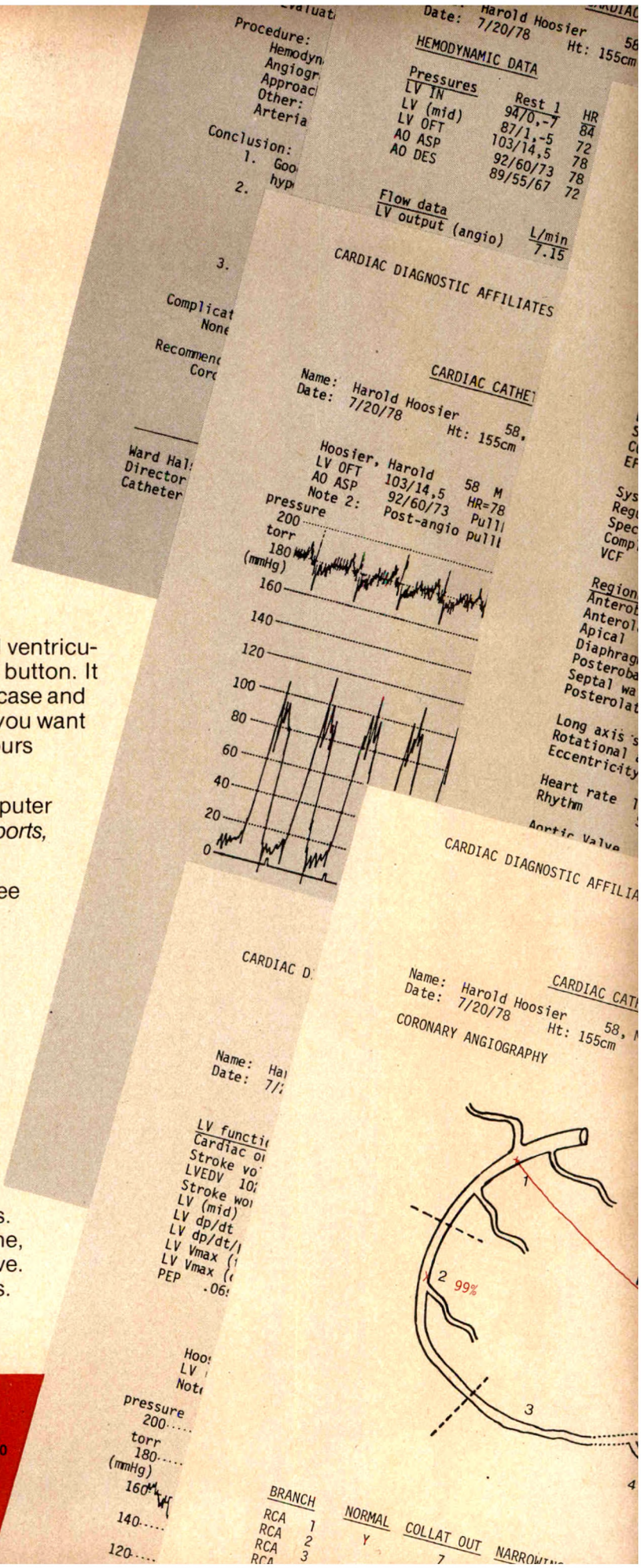
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*Reports shown are examples based on data from an actual case, using the optional IGP Printer. (All names in this advertisement are simulated; any resemblance to actual persons, living or dead, is truly coincidental.)

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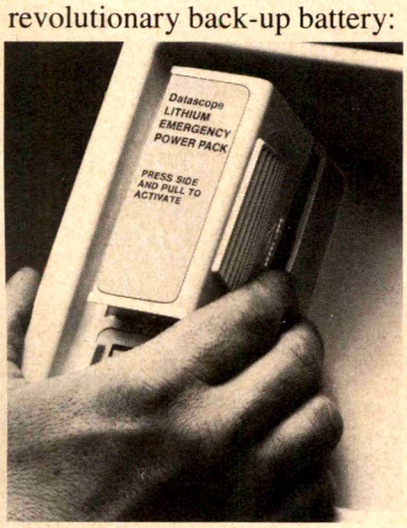
You either had too much of one thing or too little of another.

Now, you can have the best of both: the new Datascope M/D3.

The M/D3 is remarkably compact and portable. It weighs less than 25 pounds. It measures only 13″ x 15″ x 7½″. Yet it outperforms any heavy defibrillator system. And certainly any lightweight.

To start with, the M/D3 has the most advanced power system ever developed. As you might expect, the Datascope M/D3 operates on either battery or line power.

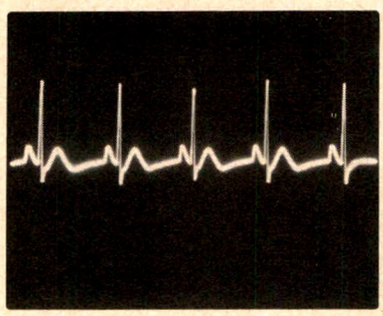
But unlike conventional systems, the M/D3 puts an end to the worry about battery failure. Because, in addition to having nickel cadmium batteries, the M/D3 also has a revolutionary back-up battery:

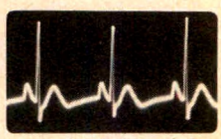


the first lithium-powered emergency pack.

We conceived the Lithium Emergency Power Pack for that emergency when your rechargeable batteries are unusable, for whatever reason. Our lithium pack needs no maintenance and remains ready for use for five years. We can't guarantee that you'll ever use it. But we can guarantee you'll be glad the first time you do.

Despite its compactness and portability, the M/D3 has a scope that measures a full 5 inches diagonally. The same size as you'd find in large systems. It has a bright non-fade display which you can freeze. And a large digital





Our scope has over 4 times the viewing area of a lightweight.

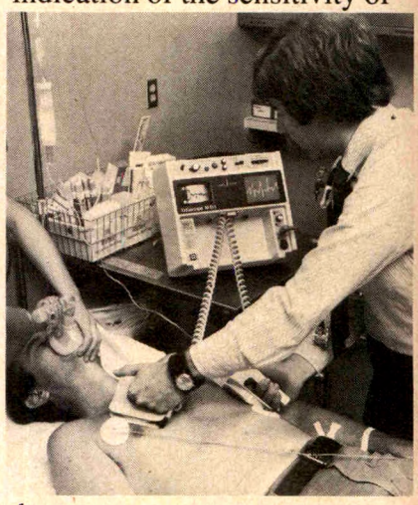
display of heart rate. And, naturally, it has the quality and performance you'd expect from the world's largest manufacturer of battery-powered monitors.

Despite its size, the M/D3 is available in a 500 joule as well as a 400 joule version. Either model incorporates a digital energy meter that precisely displays anticipated delivered energy.

Overall, the M/D3 offers those innovative details which create functional design elegance.

From the way all the operating controls are arranged in a single plane.

To the unique, dynamic calibration markers on the scope that give you an on-going indication of the sensitivity of



the trace.

To the document switch on the paddles which triggers the strip chart recorder. To the convenient way in which the paddles can be removed and replaced.

To the electrode lead fault indicator.

To the manner in which the battery pack can be rapidly ejected for replacement. To the fact that batteries are recharged in less than 5 hours instead of the usual 16.

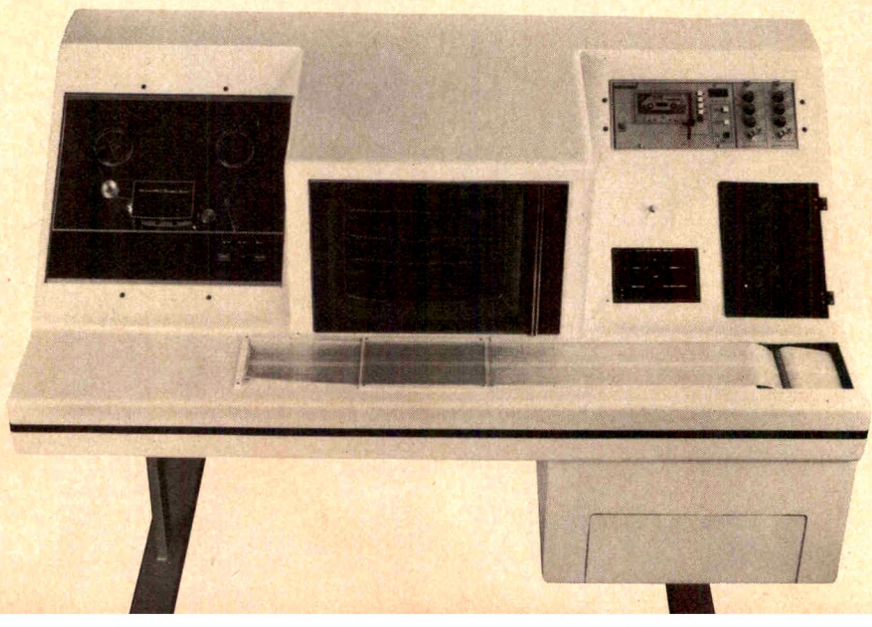
In short, the M/D3 is the most innovative development in defibrillator systems today.

Frankly, there are so many exciting features in the M/D3, there's simply not enough space to discuss them all here. We urge you to see the M/D3 first-hand. To arrange for a demonstration call us at 201-265-8800. Datascope Corp., Box 5-S , Paramus, NJ 07652.

In Europe: Datascope B.V., Post Box 26, 3870 CA, Hoevelaken, Holland.

The Datascope M/D3 Defibrillator System

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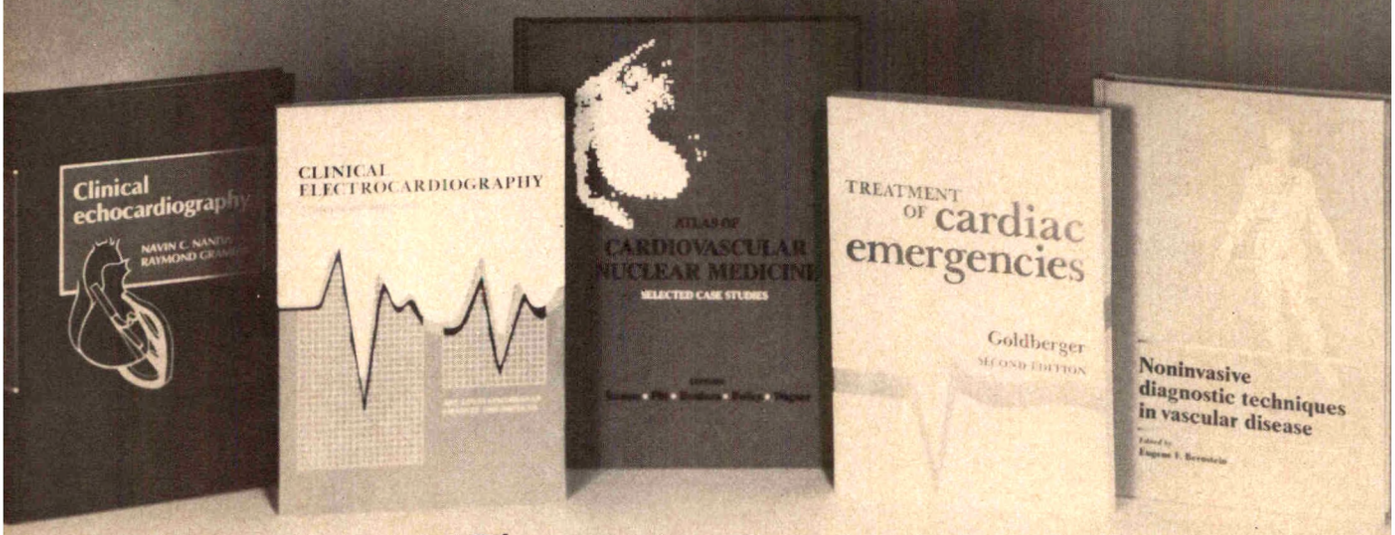
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MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see last page of this advertisement.

Practical antihypertensive therapy



for a broad range of active patients*

ALDORIL®, containing ALDOMET® (Methyldopa, MSD) and HydroDIURIL® (Hydrochlorothiazide, MSD)—two highly effective complementary agents—offers:

b.i.d. convenience for many patients

b.i.d. doses can be used for many patients.

more economical therapy

ALDORIL may offer more economical therapy than individual prescriptions for both HydroDIURIL and ALDOMET.

daily activities usually not affected

Exercise hypotension and diurnal blood pressure variations rarely occur. There is less frequent symptomatic postural hypotension than with many other antihypertensive agents.

no overshoot

Since both components of ALDORIL have a relatively short duration of action, withdrawal is followed by a return of hypertension usually within 48 hours. This is not complicated by an overshoot of blood pressure.

favorable cardiac profile

Neither component of ALDORIL usually has any direct effect on cardiac function in long-term therapy—cardiac output is usually maintained.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders.

In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

TABLETS
Aldoril® D30
containing 500 mg ALDOMET® (Methyldopa, MSD) and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
Aldoril® D50
containing 500 mg ALDOMET® (Methyldopa, MSD) and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

ALSO AVAILABLE

TABLETS
ALDORIL®-25 containing 250 mg ALDOMET® (Methyldopa, MSD) and 25 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL®-15 containing 250 mg ALDOMET® (Methyldopa, MSD) and 15 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

*As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient's needs. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

Antihypertensive TABLETS
ALDORIL® D50
methyldopa 500 mg and hydrochlorothiazide 50 mg

Antihypertensive TABLETS
ALDORIL® D30
methyldopa 500 mg and hydrochlorothiazide 30 mg

Antihypertensive TABLETS
ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS
ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation; jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. J7AR08 (021)

MSD
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detail is everything, and the key to detail in ultrasound scanners, is resolution. The finer the resolution, the clearer the detail, and the easier it is to make an accurate diagnosis of a cardiac condition.

Our new heart dedicated Sonolayergraph SSH-10A is unsurpassed when it comes to resolution, providing an ultrafine diagnostic image.



represents the state-of-the-art in highly advanced high speed ultrasonic electronic scanners. A real time cross sectional, two-dimensional "B" mode image of the heart structure can be clearly obtained by positioning the probe on the chest wall. Valve movements, chamber size and detail of the internal structures of the heart can be clearly observed, measured and diagnosed. The SSH-10A is also capable of obtaining two "M" mode tracings simultaneously as well as Kymograph* studies. With its 78° true wide angle sector range, the SSH-10A provides a permanent EKG, phono-cardiogram, and patient ID with digital caliper read-out on the CRT in the "B" mode can also be easily displayed independently on a second CRT and/or strip recorder. Additionally, the "M" mode provides four channels of physiological monitoring, EKG, phono-cardiogram, carotid pulse and apex pulse.

When it comes to providing an accurate picture of your patient's heart condition, there are two things to remember, resolution and Toshiba.

*Kymograph is a composite of "B" mode images obtained from a gated EKG.

Details about he heart you never thought possible

Toshiba's dedicated heart ultrasound, featuring ultrafine resolution and electronic phased array in real time images

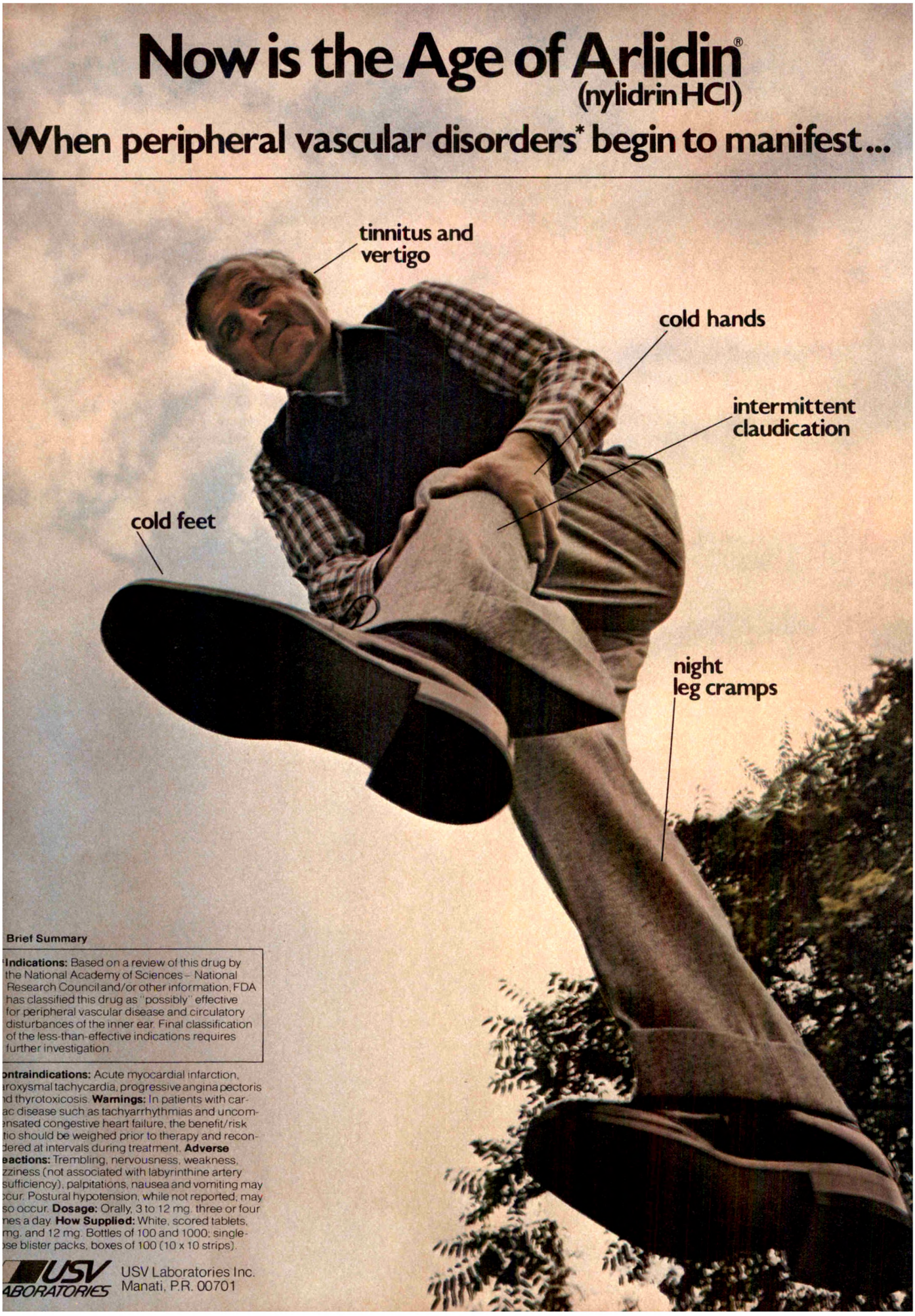


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MEDICAL SYSTEMS
In Touch with Tomorrow

Division Of Toshiba International Corporation

Now is the Age of Arlidin®
(nylidrin HCl)

When peripheral vascular disorders* begin to manifest...



Brief Summary

Indications: Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

ontraindications: Acute myocardial infarction, roxysmal tachycardia, progressive angina pectoris d thyrotoxicosis. **Warnings:** In patients with car- ac disease such as tachyarrhythmias and uncom- nsated congestive heart failure, the benefit/risk tio should be weighed prior to therapy and recon- dered at intervals during treatment. **Adverse eactions:** Trembling, nervousness, weakness, zziness (not associated with labyrinthine artery sufficiency), palpitations, nausea and vomiting may cur. Postural hypotension, while not reported, may so occur. **Dosage:** Orally, 3 to 12 mg. three or four nes a day. **How Supplied:** White, scored tablets, mg. and 12 mg. Bottles of 100 and 1000; single- se blister packs, boxes of 100 (10 x 10 strips).

USV LABORATORIES

USV Laboratories Inc.
Manati, P.R. 00701

it may be time to take these steps



Arlidin (nylidrin HCl)

Arlidin dilates responsive vessels to help increase blood flow in peripheral vascular disorders. At the same time, Arlidin helps maintain mean arterial pressure by providing an increase in cardiac output. The net effect is an increase in oxygen-bearing blood delivered to ischemic tissues, with little risk of hypotensive episodes. Therefore, symptoms of ischemia—intermittent claudication, vertigo and tinnitus, cold hands, cold feet and night leg cramps—may be relieved. And patients feel better.

Walking

The best way to get the PVD patient back on his feet is to get him on his feet. Moderate exercise, such as a therapeutic walking program, helps increase the oxygen uptake by ischemic tissues. By relieving symptoms, Arlidin may help to get the patient back on his feet; walking helps keep him on his feet.

Proper diet

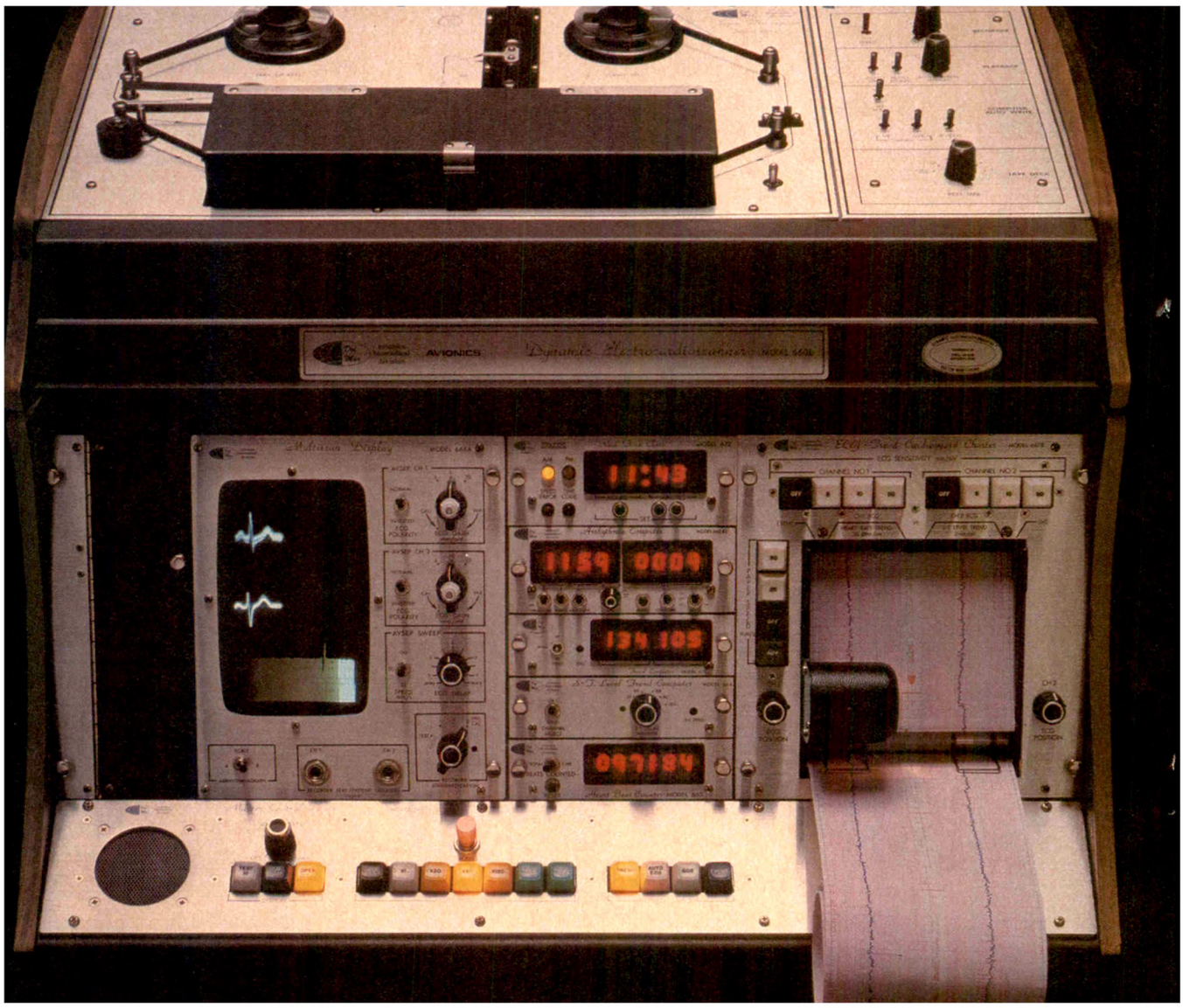
You're the best judge of what your patient should and should not eat. But, particularly for the PVD patient, caffeine should be avoided.

No smoking

The vasoconstrictive action of nicotine, as well as other damaging effects of smoking, should be made clear to the patient with peripheral vascular disease.

The new prescription for PVD*

Walking & Arlidin® (nylidrin HCl)


AVIONICS
Dynamic Electrocardiomonitor
11:43
1159
0004
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We've put the pressure on

–and more, to give you the latest in state-of-the-heart monitoring.

A new Holter Monitor—the Model 447 Electrocardiocorder®, records not only two leads of ECG data, but also up to 200 blood pressure readings from our Pressurometer® II, and encodes on tape, in digital format, the exact time of day throughout the 24-hour monitoring period.

Our other new Electrocardiocorder—the multichannel Model 448, is dedicated to recording and time-correlating implanted pacemaker pulses to the patient's ambulatory electrocardiogram. The 448 is the first Holter Monitor developed solely for the assessment of pacemaker function.

It's only natural Del Mar Avionics is first to offer you these diagnostic tools. We were first to develop practical ambulatory ECG recorders, first to utilize 2-channel recording, and first to offer 24 hours of continuous ECG information. After all, Holter Monitoring™ is our trademark.

But, this is only half the story.

The other half is our new Model 660B Electrocardioscanner®. Thread the tape, press a button and the 660B scans 24 hours of ECG and blood pressure information in 12 minutes, decoding the exact time of day directly from the tape. VE and SVE beats, heart rates, ST segment levels, and systolic/diastolic blood pressures are automatically categorized, quantified, and documented on a comprehensive trend chart.

With the trend chart completed, the 660B automatically rewinds and searches out abnormalities at 120-times real-time. Upon recognition, it precisely charts the abnormality, in real-time, with the exact time of occurrence.

You might think such advancements in "state-of-the-heart monitoring" would obsolete your current equipment. Not so! The 660B scans and analyzes recordings made on any Del Mar Avionics Electrocardiocorder. And, your Model 660 or 660A can easily be updated to a 660B.

With all these innovations, putting the pressure on is our way of being first. At Del Mar Avionics, being the first has kept us first.





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☐ 447 ☐ 448 ☐ P-II ☐ 660B

Name _____

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City _____ State _____ Zip _____

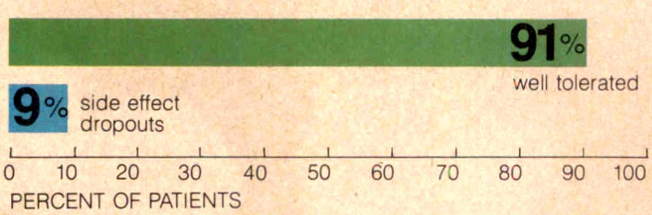
DEL MAR AVIONICS

1601 Alton Avenue at Redhill, Irvine, CA 92714, (714) 549-1500



Combipres.® There's a future in it

well tolerated—only 9% of 484 patients, in 16 clinical trials, definitely or probably dropped out due to side effects.[1]

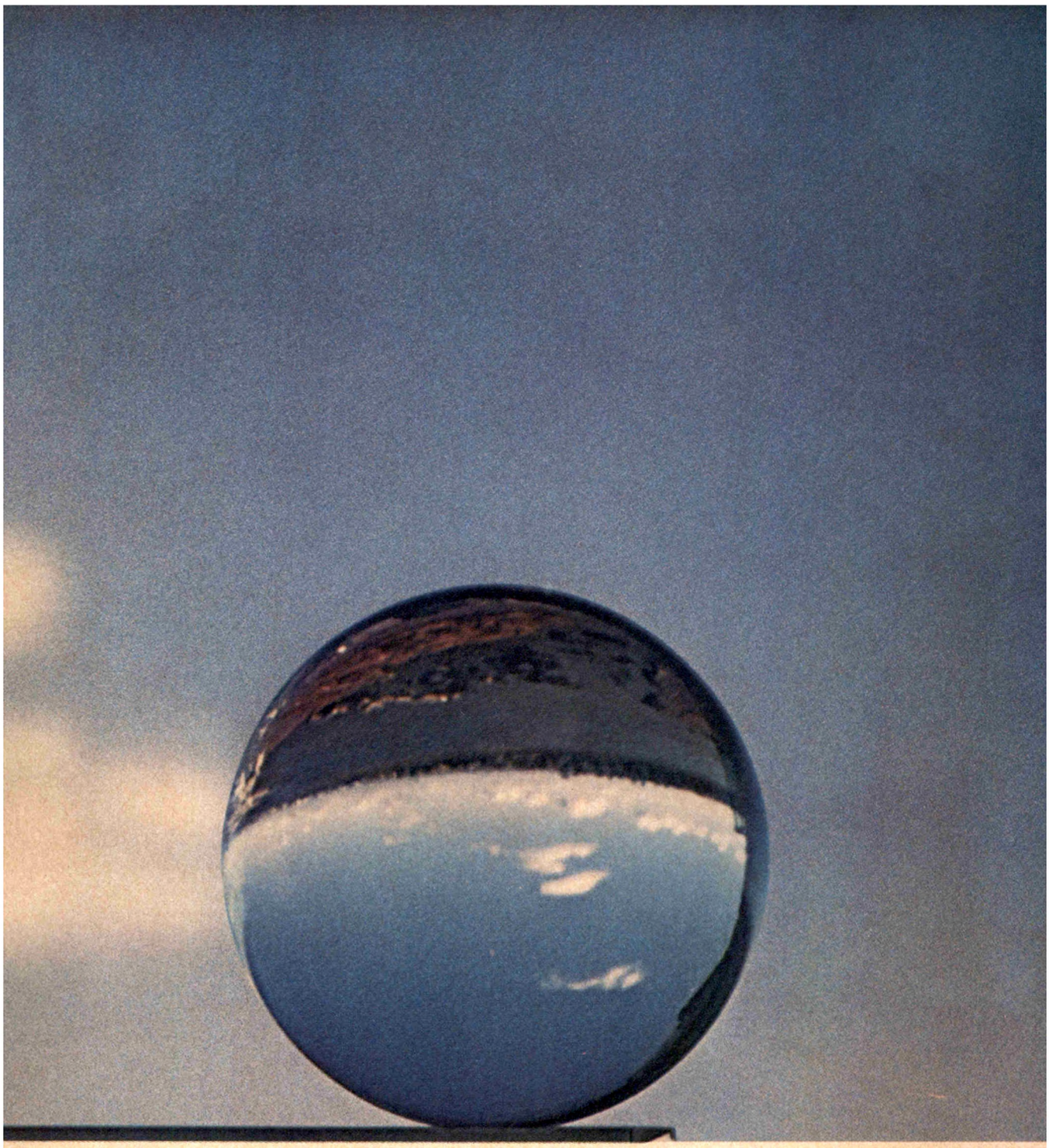


Effective control in (mild to moderate) hypertension usually with just 2 or 3 tablets daily.

Low incidence of depression, and orthostatic hypotension.*

The most common side effects are dry mouth, drowsiness, and sedation, which generally tend to diminish with time. As with other antihypertensives containing diuretic agents, hypokalemia, hyperuricemia, and hyperglycemia may occur. Drowsiness and sedation may be alleviated by giving the larger portion of the divided dose at bedtime.[2,3]

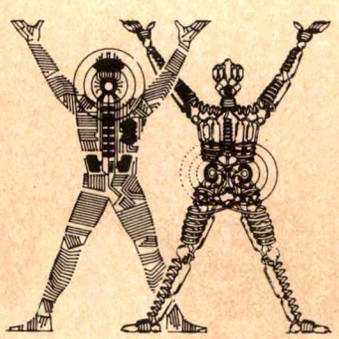
Convenient morning and bedtime dosage scheduling.



Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.

Please see brief summary of the prescribing information on the last page of this ad for warnings, precautions, and adverse reactions.

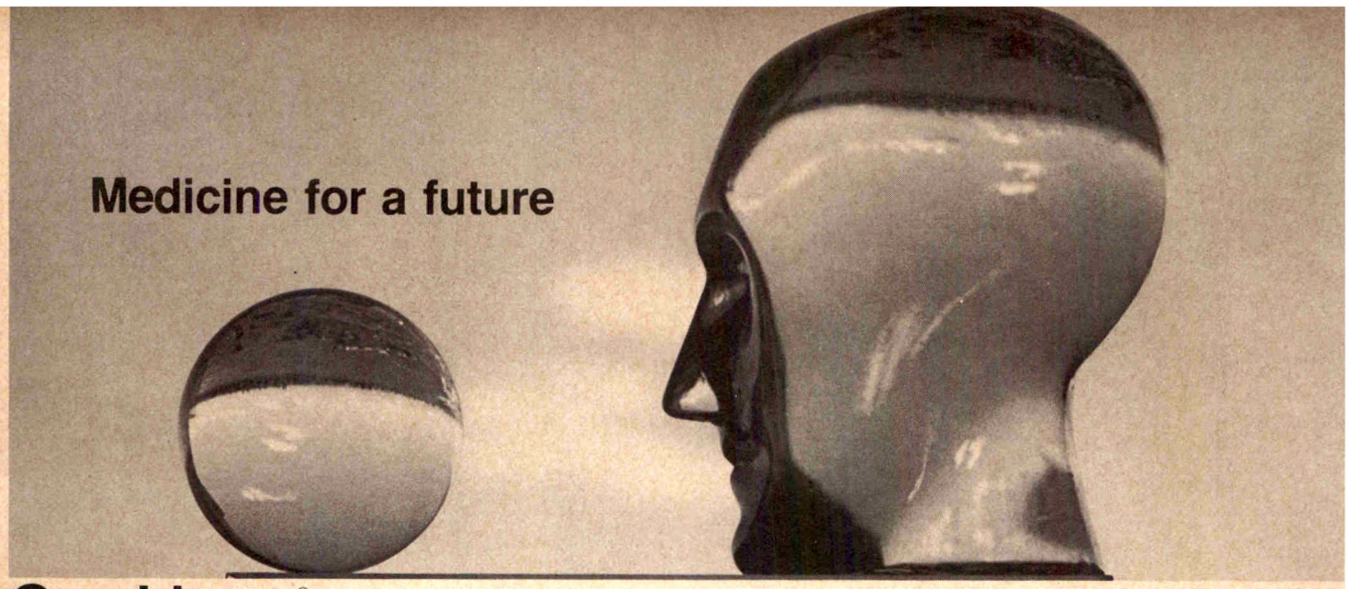


Combipres®

Each tablet contains: Catapres® (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

.1 and .2

HYPERTENSION



Combipres® .1 and .2

Each tablet contains: Catapres* (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/ day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres* 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres* 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

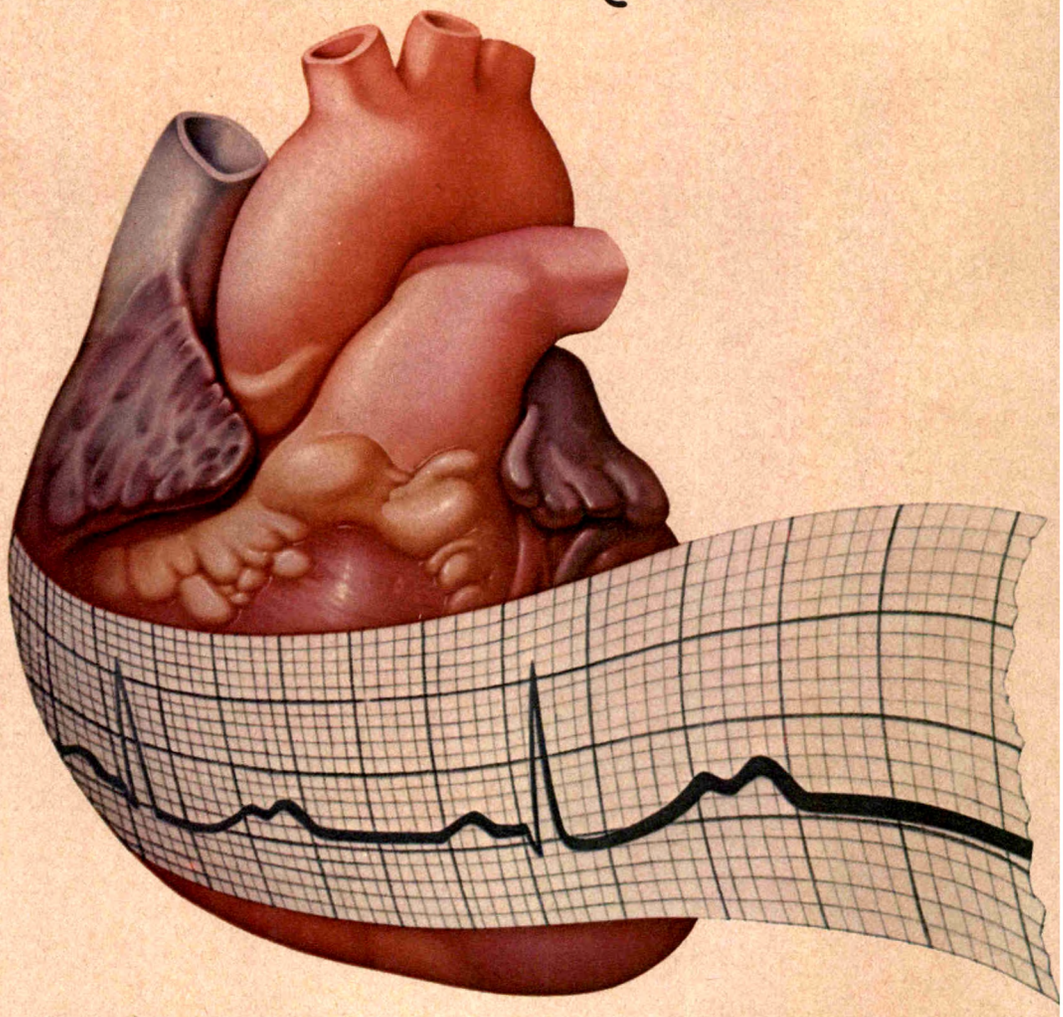
For complete details, please see full prescribing information.

References:

1. Data on file at Boehringer Ingelheim Ltd.
2. Pettinger WA: NEJM, 293:1179, 1975.
3. Katz FH: Hosp Med, *13*:34, 1977.

Boehringer Ingelheim
Boehringer Ingelheim Ltd
Ridgefield, CT 06877

WHEN THERAPEUTIC DOSES OF POTASSIUM ARE REQUIRED:



CONVENIENT AND ECONOMICAL

KAON-CL 20%®

(potassium chloride) LIQUID

40 mEq per 15 ml

Indications: KAON-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. KAON-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: In patients with hyperkalemia, chronic renal failure, systemic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Warnings: Do not administer full strength. KAON-CL 20% will cause gastrointestinal irritation if administered undiluted.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

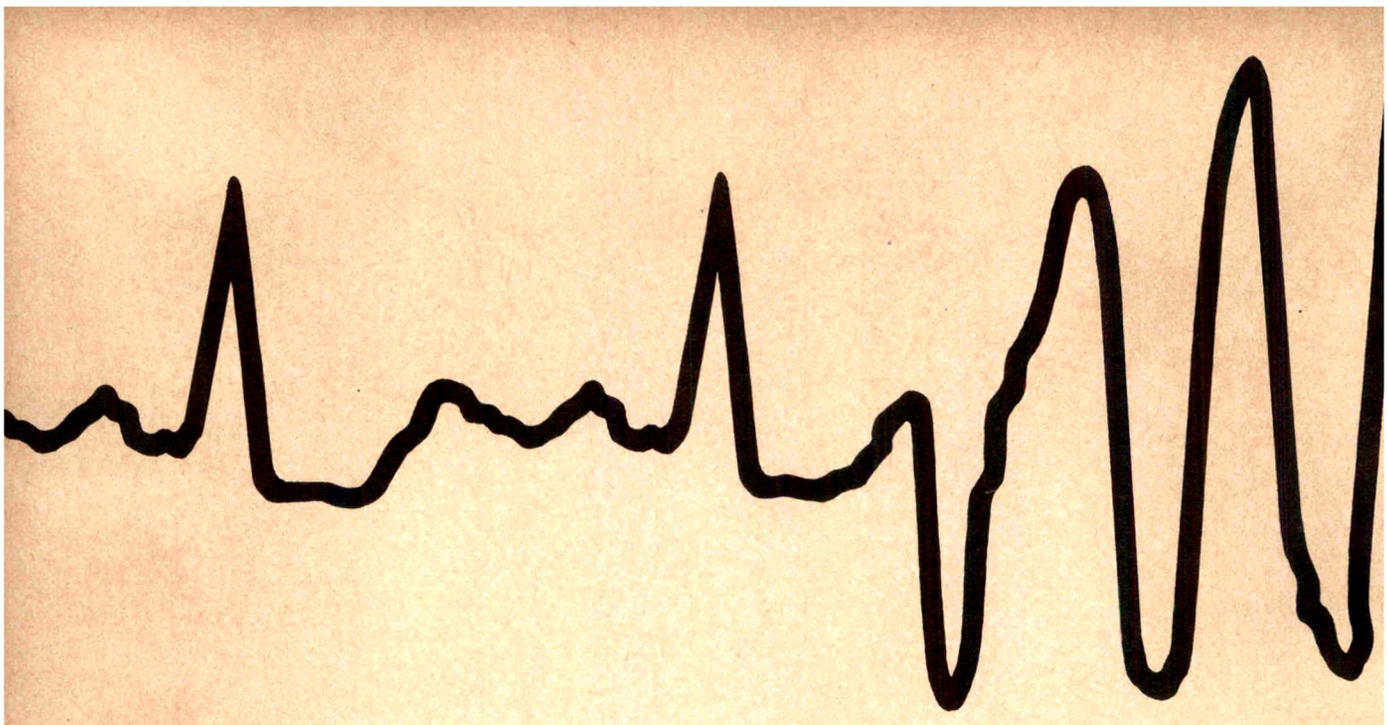
Adverse Reactions: Nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effect is hyperkalemia (see Contraindications, Warnings and Overdosage).

Overdosage: If excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes. Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

How Supplied: Pints, gallons and 4 fl. oz.

WARREN-TEED
LABORATORIES, INC.
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215



In the spirit of competition, Clinical Data would like to ask some questions about your long-term ECG (Holter) recording service.

Have they found an alternative to the error-prone, examiner-exhausting, rapid-fire Holter superimposition method?

Can they offer you a miniaturized, two-lead FM cassette recorder with a built-in timing track?

Have they ever sent you a new replacement for a malfunctioning recorder *before* you knew anything was wrong?

Do they have quality control standards for examining their examiners?

Are all their sales personnel medically trained professionals?

Do they examine recordings 'round the clock, seven days a week?

Can they convert a twenty-four hour ECG tape into a twenty-four hour report, then deliver it in less than twenty-four hours? In Los Angeles? Dallas? Chicago? New York? Philadelphia? San Francisco? Cleveland? Boston?

Do they have their own in-house engineering and research & development departments to design, maintain, and update their own equipment?

Does their report offer: Selected tracings of abnormal ECG activity? Heart rate for the entire period of recording? Examiner validated quantitation of ectopic activity by morphology? A summary of abnormal activity that can be interpreted at a glance?

If you're not sure of the answers to all of these questions, we'll give them to you. No.

Now, we freely admit that we've stacked these questions to get the desired answer. But our point is that stacking them was far too easy to do.

But Clinical Data's answers to these questions and many others is a resounding "yes." Because each of them represents a significant

Is your long-term recording servic

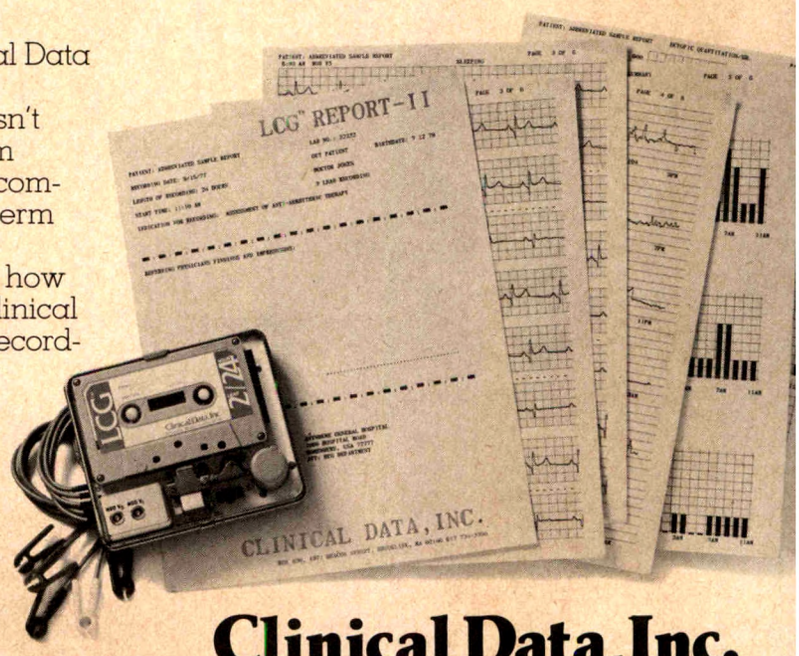
really long-term?

new development introduced by Clinical Data over the last six years.

We feel strongly that any firm that hasn't made a similar commitment to long-term recording may not be a very long-term company. Or perhaps not worthy of a long-term commitment from you.

We'd like the opportunity to show you how all our competitive edges have made Clinical Data by far the largest long-term ECG recording service in the nation — with over fifty medically trained personnel examining hundreds of millions of heartbeats and preparing thousands of reports every month.

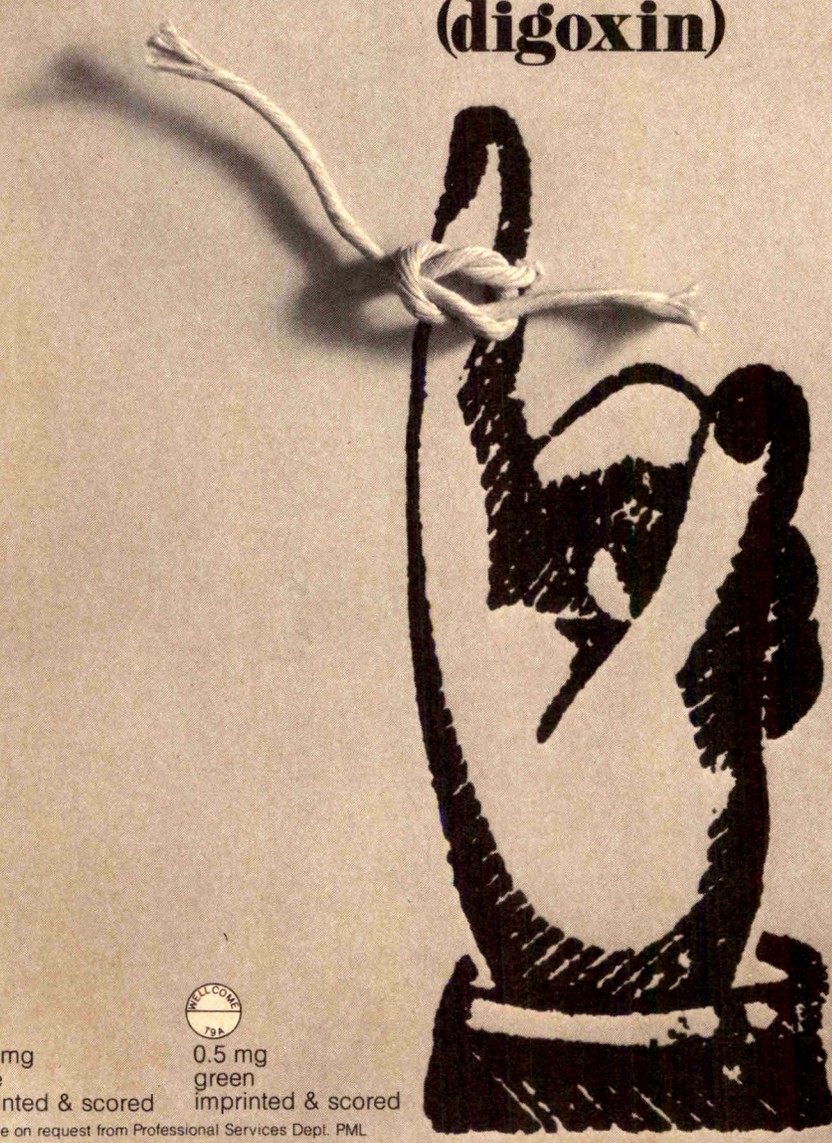
Send for our free brochure and sample LCG Report-II.™ It could be the beginning of a long-term relationship. Write to us at 1371 Beacon Street, Brookline, Massachusetts 02146. Or call toll free at 800-225-9180.



Clinical Data, Inc.

Making a long-term commitment to long-term recordin

A reminder
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(digoxin)



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yellow
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0.25 mg
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imprinted & scored

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DON W. CHAPMAN, MD, FACC

Houston, Texas

To determine the influence of coronary bypass surgery on late survival 1,144 consecutive patients were contacted 60 to 76 months after oper ation. There were 1,000 men (87.4 percent). The mean age was 50. years (range 24 to 75). Operation was performed for angina pectoris wit coronary lesions of more than 70 percent reduction in luminal diamete in 1,101 patients (96.2 percent). Forty-three patients (3.8 percent) ha congestive heart failure without angina and 240 (21.0 percent) had bot heart failure and angina. Unstable angina was present in 149 patients (1 percent). Previous myocardial infarction had occurred in 675 patients (5 percent). Single vessel disease was present in 226 patients (19.8 percent) double vessel disease in 442 (38.6 percent), triple vessel disease in 37 patients (32.9 percent) and greater than 50 percent stenosis of the lef main coronary artery in 100 patients (8.7 percent). The overall operativ mortality rate was 4.6 percent (52 patients). With exclusion of patient with left main coronary artery disease, this rate was 3.8 percent (40 o 1,044) and the overall crude 5 year survival rate was 89.1 percent (93 of 1,044). The survival rates of men and women were comparable. Lef ventricular function was classified as good if end-diastolic pressure wa less than 15 mm Hg and the left ventriculogram revealed no aneurysma or akinetic area. Among men, the respective survival rates for eac subgroup and for those with good left ventricular function within tha subgroup were as follows: *one vessel disease,* 92.9 percent (169 of 182 and 94.9 percent (130 of 137); *two vessel disease,* 90.3 percent (352 o 390) and 94.3 percent (248 of 263); *three vessel disease,* 85.7 percen (293 of 342) and 90.9 percent (189 of 208); *left main coronary arter disease,* 81.4 percent (70 of 86) and 90.6 percent (48 of 53). The graf patency rate in 157 patients was 86.4 percent (247 of 286 grafts), an 149 patients (94.9 percent) had at least one patent graft.

Late survival of all patients with reasonably good preoperative lef ventricular function was normal compared with the expected number o survivors based on the general U.S. population experience of 1973. Thus the survival rates of surgically treated patients with reasonable preop erative left ventricular function, regardless of anatomic lesions, are re stored to survival rates comparable with those of the general population With poor ventricular function, survival is impaired but is still superior t that reported with medical treatment only.

From the Department of Surgery, Baylor College of Medicine, Houston, Texas. Manuscript received April 25, 1978; revised manuscript received June 6, 1978, accepted June 7, 1978.

Address for reprints: Gerald M. Lawrie, MD, Department of Surgery, Baylor College of Medicine, Houston, Texas 77030.

ABLE I

urvival in Overall Group and Subgroups

	Patients (no.)	Deaths (no.)		Mortality Ratio (actual/expected)	Actual Survival as Percent of Expected Survival
		Actual	Expected		
verall group					
Men	1,000	116	79.4	1.46	96%
Women	144	14	7.0	2.00	95%
Total	1,144	130	86.4	1.50	96%
V disease*					
Good LV	137	7	9.3	0.75	102%
Poor LV	45	6	3.4	1.76	94%
Total	182	13	12.7	1.02	100%
V disease*					
Good LV	263	15	20.5	0.73	103%
Poor LV	127	23	10.2	2.25	89%
Total	390	38	30.7	1.24	98%
V disease*					
Good LV	208	19	17.9	1.06	99%
Poor LV	134	30	10.3	2.91	84%
Total	342	49	28.2	1.74	93%
2, 3 V disease*					
Good LV	608	41	47.8	0.86	101%
Poor LV	306	59	23.9	2.47	88%
& 3 V disease*					
Good LV	471	34	38.4	0.89	101%
Poor LV	261	53	20.5	2.59	86%
ft main disease*					
Good LV	53	5	5.0	1.00	100%
Poor LV	32	11	2.9	2.64	72%
Total	86	16	7.9	2.03	90%

* Data based on male patients only.
LV = left ventricular function; V = vessel.

lthough the coronary bypass operation has gained ide acceptance as a highly effective therapy for angina ectoris,[1,2] its influence on the longevity of patients with ultivessel coronary disease has remained uncertain xcept in the small group of patients with stenosis of the ft main coronary artery in whom it has been shown to roduce superior late survival rates.[3,4]

The aim of this study was to determine the influence f the coronary bypass operation on the late survival of a large group of patients with multivessel coronary disease who were followed up for more than 5 years.

ABLE II

erioperative Mortality and Absolute Overall 2 and 5 Year urvival Rates in Men with One, Two and Three Vessel isease

	Perioperative Mortality (30 day)	Overall 2 Year Survival	Overall 5 Year Survival
V disease			
Good LV	0.7% (1/137)	97% (133/137)	95% (130/137)
Poor LV	4.4% (2/45)	91% (41/45)	87% (39/45)
Total	1.6% (3/182)	96% (174/182)	93% (169/182)
V disease			
Good LV	1.1% (3/263)	97% (255/263)	94% (247/263)
Poor LV	4.7% (6/127)	89% (113/127)	82% (104/127)
Total	2.3% (9/390)	94% (368/390)	90% (351/390)
V disease			
Good LV	4.8% (10/208)	94% (196/208)	91% (189/208)
Poor LV	9.0% (12/134)	84% (112/134)	78% (104/134)
Total	6.4% (22/342)	90% (308/342)	86% (293/342)

LV = preoperative left ventricular function; V = vessel.

Material and Methods

Clinical data: Between March 1971 and December 1972, a total of 1,144 consecutive patients underwent saphenous vein aortocoronary bypass graft operations at our institution. These data do not include the 31 patients who received prosthetic heart valves. There were 1,000 men (87.4 percent) and 144 women (12.6 percent) with a mean age of 50.1 years (range 24 to 75).

The indications for the 1,144 operations were symptoms of stable angina pectoris in 952 patients (83.2 percent), unstable angina in 149 (13 percent), angina plus congestive heart failure in 240 (21 percent), and congestive heart failure without angina in 43 (3.8 percent). A history of previous myocardial infarction was given by 675 patients (59 percent). A detailed analysis of the preoperative findings in many of these patients has previously been reported.[5,6]

Angiographic data: A lesion of more than 70 percent reduction in luminal diameter was present in a single coronary vessel in 226 of the 1,144 patients (19.8 percent), in two vessels in 442 (38.6 percent) and in three vessels in 376 (32.9 percent). Left main coronary stenosis of more than 50 percent was present in 100 patients (8.7 percent).

Preoperative left ventricular function was classified as either good or poor on the basis of the preoperative left ventricular end-diastolic pressure and ventriculogram. Good left ventricular function was defined as the presence of an end-diastolic pressure of less than 15 mm Hg and the absence of an akinetic or aneurysmal area in the left ventriculogram. Poor left ventricular function was defined as an end-diastolic pressure of more than 15 mm Hg or a contraction abnormality

as defined, or both. Patients with increased end-diastolic pressure (up to 55 mm Hg) were not excluded. Further subjective evaluation of the left ventriculogram by visual estimation of end-diastolic volume, ejection fraction or myocardial contractility was not employed in classifying left ventricular function. Unfortunately, in this early experience, objective measurements of the ejection fraction were not available. Cardiomegaly as defined by the cardiothoracic ratio in the chest X-ray film was not used as an index of left ventricular function.

By the objective criteria defined, left ventricular function was reasonably good in 775 (67.7 percent) of the 1,144 patients and poor in 369 (32.3 percent). Of these 369 patients, 117 (31.7 percent) had an end-diastolic pressure of 25 to 55 mm Hg; a left ventricular aneurysm consisting of an area of paradoxic motion as shown with left ventriculography was present in 27 (7.3 percent); resection of a left ventricular aneurysm was performed in 11 (3.0 percent). Thus, no patient was excluded retrospectively from this series, regardless of the severity of impairment of left ventricular function. Had we used the additional criteria of ventricular function mentioned, only 28.6 percent (327 of 1,144) of patients would have had normal left ventricular function.

Surgical technique: All patients received one or more reversed saphenous vein aortocoronary bypass grafts performed with normothermic ischemic arrest and hemodilution prime total cardiopulmonary bypass. These techniques have previously been reported in detail.[5,6]

Follow-up: The survival rate of 1,124 patients was determined more than 5 years after operation in all cases. Follow-up was therefore 98.3 percent (1,124/1,144) complete after 5 years. Patient survival was determined from office charts, by letter, by telephone calls and finally with use of professional investigators.

Statistical analysis: From the follow-up data obtained, we determined the absolute number and time of death of these patients from all causes. We could then determine the absolute crude 5 year survival rate, overall and for each patient group (Tables I and II). From a knowledge of each patient's age at operation and the number of years he survived, we calculated the exposure to the risk of death of each of the 1,144 patients, defining exposure as the total number of years lived at each age by the lives in the study. Thus, a subject who survived 5 years contributed 1 life year of exposure at each of five ages, whereas a subject who died during the 5 year interval contributed 1 life year of exposure for each year from the year of operation to the year in which death occurred, inclusive. Having determined the exposure, we applied the mortality rates by sex for the general U.S. population at each attained age to the total life years of exposure in each group and subgroup. This gave the expected number of deaths and thus the expected survival rate for each patient group (Table I). This expected survival rate was defined as the normal survival rate for the patients in this study.

The expected mortality rates were based on the general U.S. population experience of 1973.[7] This year was chosen because it corresponded to the mean time of death of the patients in this study. From a knowledge of the actual and the expected number of deaths in each group, a mortality ratio of actual to expected deaths was calculated for each group. When more than 35 deaths had occurred in a group, the mortality ratios were assumed to be normally distributed. For these groups an upper confidence limit at the 95 percent level was calculated for the ratio of actual to expected deaths, and the corresponding number of deaths and survivors was calculated for this confidence limit. The statistical method used is reported in detail elsewhere.[8] The survivor totals calculated were then compared with the number of survivors expected from the experience of the general U.S. population, for comparison with the observed ratios of actual survivors to expected survivors (Table III).

Results

The survival data for the overall group are summarized in Tables I and II. The perioperative mortality rate within 30 days of operation was 4.6 percent (52 of 1,144) overall and 3.5 percent (40 of 1,144) with exclusion of patients with left main coronary stenosis. The absolute crude 5 year survival rate (including perioperative mortality) was 88.6 percent. This was 96 percent of the expected normal survival rate for the overall group. Men and women had similar late survival rates, 96 and 95 percent of normal, respectively (Table I, Fig. 1). Because of this similarity, and their small numbers, women were excluded from further detailed analysis.

TABLE III

Calculated Mortality Ratios and Number of Survivors at Upper Confidence Limit of 95 Percent

	Observed Mortality Ratio	Upper Confidence Limit (95%)	Calculated no. of Survivors at Upper Confidence Limit	Calculated no. of Survivors as Percent of Expected Survivors
Overall	1.50	1.72	995.4	94%
2 V disease*	1.24	1.58	341.5	95%
3 V disease*	1.74	2.15	281.4	90%
1, 2, 3 V disease				
Good LV	0.86	1.09	555.9	99%
Poor LV	2.47	3.00	234.3	83%
2 & 3 V disease				
Good LV	0.89	1.15	426.8	99%
Poor LV	2.59	3.18	195.8	81%

* Male patients only.

LV = preoperative left ventricular function; V = vessel.

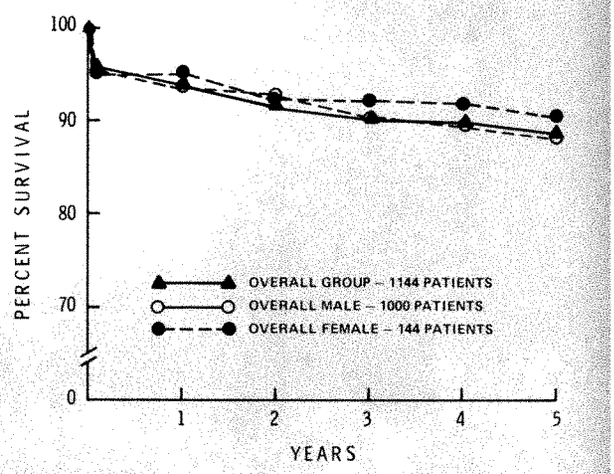


FIGURE 1. Survival of overall group in the study. The late survival rates of men and women are almost identical.

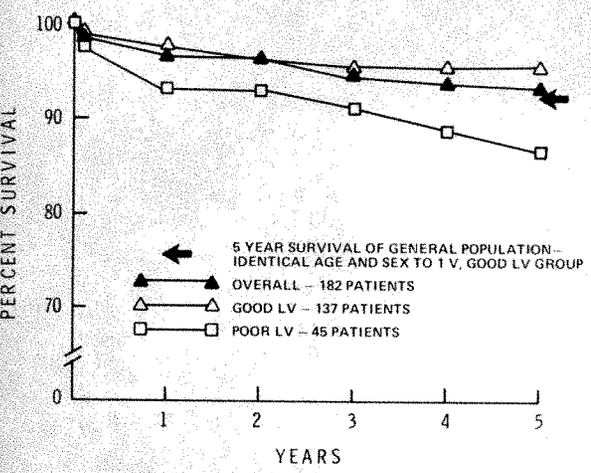


FIGURE 2. Survival of men with single vessel (1 V) disease according to preoperative left ventricular (LV) function. The expected 5 year survival rate of a sample group from the general U.S. population of identical age and sex distribution is indicated **(arrow)**.

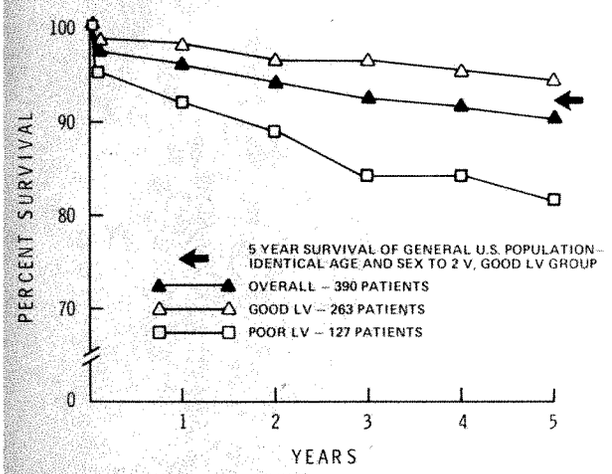


FIGURE 3. Survival of men with double vessel (2 V) disease according to preoperative left ventricular (LV) function. Data from the general population as in Figure 2.

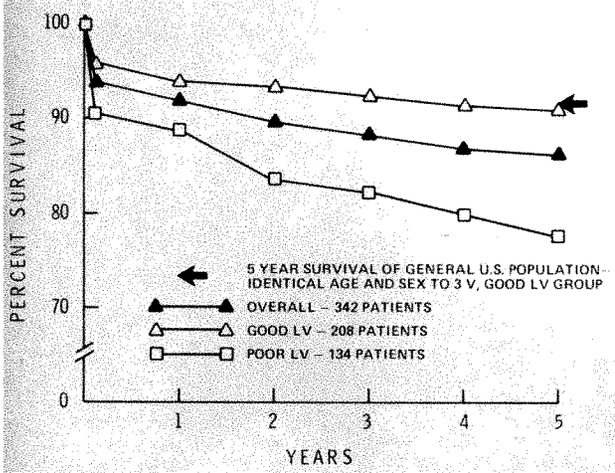


FIGURE 4. Survival of men with triple vessel (3 V) disease according to preoperative left ventricular (LV) function. Data from the general population as in Figure 2.

Survival related to extent of coronary artery disease: It is apparent from Table I and Figures 2 to 6 that patients with single, double or triple vessel disease or left main coronary artery disease who had reasonably good preoperative left ventricular function had normal rates of survival past 5 years in relation to the general U.S. population. Survival was decreased in all patients with poor left ventricular function, in part because of a significant operative mortality (which is substantially lower in current experience).

Survival related to left ventricular function: By grouping the patients according to preoperative left ventricular function without regard to the number of diseased vessels preoperatively, it was possible to demonstrate that after coronary bypass, the principal determinant of survival beyond 5 years was the preoperative status of left ventricular function, not the number of vessels diseased. The survival rate for patients with good left ventricular function was normal

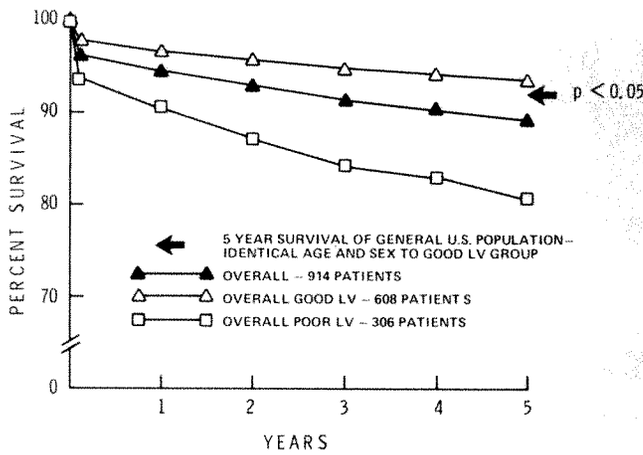


FIGURE 5. Survival of all men according to preoperative left ventricular (LV) function (patients with left main coronary stenosis excluded). Data from the general population as in Figure 2.

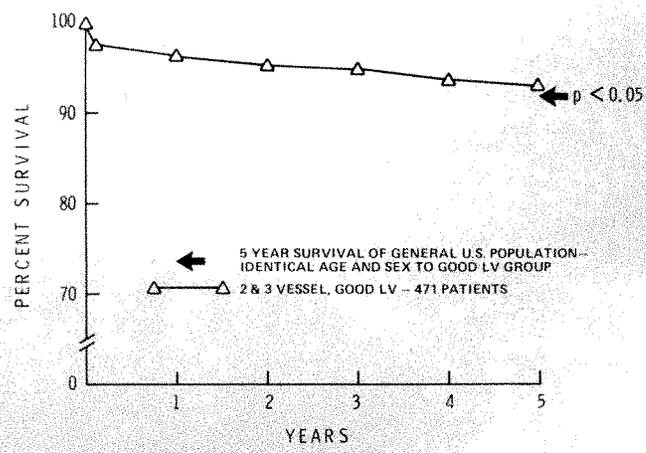


FIGURE 6. Survival of men with double and triple vessel disease and good left ventricular (LV) function. Data from the general population as in Figure 2.

(93.3 percent; 567 of 608) (Fig. 5), whereas patients with poor left ventricular function had a survival rate of 80.7 percent (247 of 306). Even excluding single vessel disease, patients with two and three vessel disease and reasonably good left ventricular function had a normal survival rate (95 percent confidence limit) (assuming a normal mortality ratio distribution even though there were only 34 deaths in this group) (Fig. 6, Tables I and II).

Graft patency: This was determined in 157 patients 0 to 70 (mean 26.4) months postoperatively. The overall graft patency rate was 86.4 percent (247 of 286). Bypass grafts to the left anterior descending coronary artery had a patency rate of 88.3 percent (121 of 137), whereas the patency rate was 84.6 percent (77 of 91) for the right and 84.5 percent (49 of 58) for the circumflex coronary arteries. All grafts were patent in 121 (77.1 percent) of the 157 patients, and 149 patients (94.9 percent) had at least one patent graft. The average number of grafts per patient was 1.0 for one vessel disease, 1.8 for two vessel disease and 2.2 for three vessel disease. Patients with left main coronary arterial stenosis received an average of 2.0 grafts.

Discussion

Design of the study: In our study, the survival of our surgical patients was compared with that of the rest of the general U.S. population of which they formed a part, rather than with a separate nonrandomized medical control group. To enhance the significance of the results we included all patients treated primarily for coronary disease in our consecutive series of 1,144 patients regardless of the severity of the preoperative clinical status or the degree of impairment of left ventricular function. Both elective and emergency operations were included in the series. We included deaths from all causes, including even those clearly not related to a cardiac event, such as death from cancer or accidents. Thus, we eliminated the risk of retrospective selection of a good risk patient population from our overall experience. Furthermore, although initially our group of patients was free of other serious diseases such as cancer, the 5 year interval of follow-up was sufficiently long to provide an exposure of our group to the risk of these diseases comparable with the risk of the general population. This was demonstrated particularly well in relation to cancer: The six deaths definitely established as due to cancer during the study in our 1,144 patients represented an annual incidence of 105/100,000, a figure comparable with that of 167.3/100,000 for the general population. In 1,144 patients, this difference would be only 3.6 patient deaths in 5 years. Furthermore, other chronic illnesses that would have excluded patients from consideration for operation, such as severe chronic pulmonary disease (annual mortality rate 26/100,000), hepatic disease (15/100,000) or renal insufficiency (7/100,000), together account for only 48/100,000 per year, which in our study would have added only 2.8 deaths to the total number expected over the entire 5 year interval. We believe any other slight imbalance due to selection in the 1st year of the study are overwhelmingly compensated for by the fact that coronary artery disease is by far the most common cause of death in the general population, with an incidence of 360/100,000.[7]

We elected to follow up a large group of patients for more than 5 years to be able to determine absolute 5 year survival rates and avoid recourse to a complex actuarial analysis. We were thus confined to reviewing the fate of patients operated on between 1971 and 1972 when our surgical results, although good for their time, were not representative of our later results, which have improved consistently over the last 6 years despite poorer clinical material. Our approach enabled us to obtain subgroups of adequate size and duration of follow-up for meaningful analysis. We chose coronary lesions of greater than 70 percent to ensure that truly severe coronary disease was present in each category.

Survival rates compared with 1973 U.S. population data: The selection of the mortality experience of the general U.S. population of 1973 enabled us to compare our mortality with that of the same population from which our patients were derived and of which they continued to constitute a portion. Furthermore, because the greatest incidence of mortality was in the first 12 months of our study, 1973 represented the mean time of death for the entire study period, 1971 to 1977.

Because cardiovascular mortality in the general U.S. population has been decreasing since 1963 it was important to compare survival rates with those in the appropriate sample of the general U.S. population. The figure for the expected deaths for each group was calculated from the age and sex of each individual patient in the study and is not a rough approximation based on the mean age of each group but an exact application of the actual mortality experience of the 1973 general U.S. population to the exposure determined for our individual patients. In addition, this comparison was made not with the mortality rates for a population sample with known cardiovascular disease but for the entire general U.S. population. In view of these observations we were interested to find that patients with reasonably good (but not necessarily normal) preoperative left ventricular function (68 percent of our study group) achieved a normal survival in relation to the general U.S. population.

Determinants of postoperative survival: That the coronary bypass grafting is responsible for this restoration of survival to normal is further suggested by the convergence to a normal survival rate of all subgroups with good left ventricular function, including those with double and triple vessel disease and left main coronary arterial stenosis. The principal determinant of survival after coronary bypass surgery in our study was the status of preoperative left ventricular function; the number of vessels diseased preoperatively influenced only perioperative mortality, not late survival.

These results suggest to us that coronary bypass surgery does favorably influence late survival and that improved late survival rates occur because the coronary bypass grafts effectively eliminate the functional significance of proximal coronary lesions. Thus, as we have

eported previously,[9] the status of the majority of pat-nts with double or triple vessel disease or left main oronary arterial stenosis is converted by operation to ne functionally equivalent to that of no significant oronary lesion or to single vessel disease, both of which ave a good prognosis. We have demonstrated previ-usly that patients with two residual lesions after op-ration have a poorer survival than patients with good evascularization.[9] The survival of our patients with ignificant preoperative left ventricular impairment was t least as good as previously reported with medical herapy.[10–14] Although we now have preliminary evi-ence from isotope ventriculography of improved left entricular function after coronary bypass surgery unpublished data), it is clear that such surgery cannot estore normal function to a severely scarred ventri-le.

Comparison with previous published reports: In detailed clinical follow-up[15] of 434 consecutive pa-ients operated on between 1968 and 1971, immediately efore our present study group, we documented the elative stability of ventricular function, the native oronary circulation and graft patency after 5 years. ate histologic and angiographic studies[16–18] of the vein rafts also have shown good long-term benefits in almost ll cases.

Our conclusions are at variance with those recently eported in the Veterans Administration Cooperative tudy.[19] We have previously reported in detail[9,15] our iews as to why that study has failed to show improved urvival in surgically treated patients. We believe the rincipal reasons for the relatively poor late surgical urvival in that study were (1) the high perioperative ortality rate of 5.6 percent experienced in a good risk roup of patients, and (2) the low graft patency rate of 9 percent, with 88 percent of patients having at least ne patent graft but only 54 percent having all grafts atent, compared with our respective figures of 86.4, 4.9 and 77.1 percent. Among patients with two and hree vessel disease, only 41.3 percent (62 of 150) of hose with double and triple bypass grafts had all grafts atent in the Veterans Administration study compared ith 73.1 percent (95 of 130) in our experience. Many atients in the Veterans Administration study must ave had at least the equivalent of two vessel residual disease after operation and thus remained in a high risk survival category.

Implications of study: We have demonstrated here, and previously,[9] that, provided preoperative left ventricular function is reasonably good, survival can be restored to normal by revascularization of the three major vessel systems. These findings, together with the persistent symptomatic relief we have observed in more than 90 percent of our patients, make us question seriously the necessity for more than three (or at most, four) bypass grafts to be performed in any one patient. The current fashion for performing up to eight or nine bypass grafts is based on an extrapolation of the improved survival observed when lesions in the three major vessels are all bypassed. There are as yet no data available demonstrating above normal survival with large numbers of grafts. Nor has the long-term patency rate of grafts to small secondary and tertiary coronary branches been established. Furthermore, patients who have good coronary arteries capable of receiving multiple grafts clearly have a prognosis superior, for example, to that of a patient with multivessel coronary disease in whom it is technically feasible to graft only one or two vessels.

The results of our study suggest to us that, provided an adequate number of patent grafts are established at a low operative risk, patients with multivessel coronary disease and reasonably good preoperative left ventricular function can be restored to a normal chance of survival more than 5 years after operation. Thus, because the quality of surgery is a critical determinant of late survival, it is important that the rates of perioperative mortality, perioperative infarction and graft patency of each surgeon be reviewed. The cardiologist as well as the surgeon must play an active role in this regard. Only in this way can patients be assured that they will obtain from the coronary bypass operation the benefits not only of symptomatic relief but also of improved survival.

Acknowledgment

We are indebted to James D. Brock, CLU, Actuarial Director, and Donald G. Southwell, FSA, Associate Actuarial Director, Prudential Insurance Company of America, for invaluable assistance with analysis of the survival data in this study.

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Relation of Graded Exercise Test Findings After Myocardial Infarction to Extent of Coronary Artery Disease and Left Ventricular Dysfunction

THOMAS D. PAINE, MD
LARRY E. DYE, MD
DAVID I. ROITMAN, MD
J. THOMAS SHEFFIELD, MD, FACC
CHARLES E. RACKLEY, MD, FACC
RICHARD O. RUSSELL, Jr., MD, FACC
WILLIAM J. ROGERS, MD, FACC

Birmingham, Alabama

To evaluate the effectiveness of the graded exercise test in predicting the extent of coronary artery disease and the degree of left ventricular dysfunction in patients with prior myocardial infarction, 100 consecutive patients underwent both graded exercise testing and coronary and left ventricular angiography at a median of 4 months after infarction. The studies caused no complications. An equal number of patients had anterior and inferior infarction. Coronary artery disease, defined as 70 percent or greater stenosis of luminal diameter, was present in three vessels in 31 patients, in two vessels in 35 patients, in one vessel in 33 patients and in no vessel in one patient. With "diagnostic" electrocardiographic criteria of 1 mm or greater J point depression plus a flat or downsloping S-T segment, 31 patients had an electrocardiographically positive exercise test; 27 of these (87 percent) had two or three vessel coronary artery disease. Of the 21 patients with a negative exercise test, 62 percent had coronary artery disease in no more than one vessel, 33 percent in two vessels and 5 percent in three vessels. Fourteen patients had S-T segment elevation during exercise; these patients had a lower ejection fraction and larger angiographic scar size than the remaining 86 patients. Patients terminating exercise because of symptoms of left ventricular dysfunction (fatigue or dyspnea) showed correlation between duration of exercise and ejection fraction ($r = 0.65$) and between duration of exercise and angiographic scar size ($r = -0.62$). Thus, several months after infarction, the graded exercise test can be performed safely and can be utilized to predict the extent of coronary artery disease and left ventricular dysfunction in selected groups of patients.

From the Division of Cardiology, Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama. This research was supported in part by Contract 5P50HL 17667-03 (Specialized Center of Research for Ischemic Heart Disease), by Program Project Grant HL 1,310, National Heart, Lung, and Blood Institute and by Clinical Research Unit Grant MO-RR000-13 (General Clinical Research Centers Program, Division of Research Resources), National Institutes of Health, Bethesda, Maryland. Manuscript received April 11, 1978; revised manuscript received June 13, 1978, accepted June 14, 1978.
Address for reprints: William J. Rogers, MD, Division of Cardiology, Department of Medicine, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294.

The diagnosis and treatment of coronary artery disease has been revolutionized by the availability of coronary angiography and coronary revascularization surgery. Studies have shown that the extent of coronary artery disease and the degree of left ventricular dysfunction correlate inversely with longevity[1–4] and that revascularization surgery in selected patients may prolong life.[5–10]

Although it can be assumed that almost all patients with acute myocardial infarction have occlusive coronary artery disease, some have only localized stenoses in the coronary arteries supplying the infarcted zone, whereas others have significant stenoses in multiple coronary vessels, including those supplying viable myocardium. Identification of the latter group of patients may be important in their long-term management, but currently coronary angiography is not generally recommended as a routine diagnostic procedure in all patients after myocardial infarction.[11]

The graded exercise test is a safe, readily available and relatively inexpensive diagnostic procedure, known to be useful in predicting the extent of coronary artery disease in patients with angina pectoris.[12–19] This study was undertaken to determine if the graded exercise test, performed in patients several months after myocardial infarction, might be a useful screening procedure to predict the extent of coronary artery disease and the degree of left ventricular dysfunction.

Methods

Patients: Records of patients admitted to the Clinical Research Center of the University of Alabama Medical Center for diagnostic coronary arteriography from August 1971 to March 1977 were reviewed to find consecutive patients satisfying the following criteria: (1) definite evidence of prior myocardial infarction, manifested either by documented evolutionary electrocardiographic and serum enzyme changes on a prior admission or by unequivocal evidence of prior infarction on the current electrocardiogram, or both; (2) technically satisfactory coronary arteriographic and quantitative left ventriculographic studies; (3) graded exercise test performed within 2 days of coronary arteriography; and (4) no evidence of congenital or significant valvular heart disease. Patients with unstable angina or severe congestive heart failure were excluded from this study because exercise testing is contraindicated in such patients.

Routine clinical evaluation: All subjects underwent a complete medical history and physical examination by two examiners. The severity of exertional angina and congestive heart failure was graded according to the classification of the Canadian Cardiovascular Society,[20] and the New York Heart Association,[21] respectively.

Graded exercise tolerance testing: Exercise testing[22] was performed 2 or more hours postprandially. Before exercise, blood pressure (supine, sitting and standing) was recorded, a standard 12 lead electrocardiogram was performed with the patient supine and at rest, and informed consent was obtained. Conventional leads V_4 to V_6 and Frank X, Y and Z leads were recorded with the patient supine and standing.

Treadmill exercise was conducted in 3 minute uninterrupted stages using the following treadmill settings[23]: Stage I—speed 1.7 miles/hour and 10 percent grade; stage II—2.5 miles/hour and 12 percent grade; stage III—3.4 miles/hour and 14 percent grade; stage IV—4.2 miles/hour and 16 percent grade; stage V—5.0 miles/hour and 18 percent grade; and stage VI—5.5 miles/hour and 20 percent grade. Blood pressure was recorded at 2 minute intervals during and after exercise. Leads V_4 to V_6 and Frank leads X, Y and Z were recorded during each 3 minute stage of exercise, at the end of exercise and every 2 minutes after exercise for 6 minutes.

Graded exercise test was terminated if (1) 90 percent of the predicted maximal heart rate for age was reached[24]; (2) chest pain, claudication, exaggerated fatigue or dyspnea, symptoms of cerebral insufficiency or hypotension developed; or (3) the electrocardiogram showed intraventricular conduction defect, arrhythmia or ischemic S-T segment changes as defined later.

The graded exercise test was interpreted as negative, positive or inconclusive according to the following criteria (Table I): The test was graded *negative* when 90 percent of the predicted maximal heart rate for age was achieved, the S-T segments were essentially isoelectric and no chest pain occurred during or after exercise. *A positive test* was subcategorized as electrocardiographically or clinically positive. A test was judged *electrocardiographically positive* when a subject with isoelectric S-T segments at rest manifested in any recorded lead 1 mm or more horizontal or downsloping S-T segment changes during or after exercise. In subjects having abnormal S-T segments at rest, S-T segment depression of 2 mm or more during or after exercise constituted a positive graded exercise test.[25] For patients receiving digitalis, S-T depression of 2 mm or more during or after exercise plus concurrent angina was required for an electrocardiographically positive test (three patients). A test was judged *clinically positive* when subjects experienced chest pain characteristic of angina pectoris but had no concurrent diagnostic S-T changes. A test was considered *inconclusive* when subjects terminated exercise before achieving 90 percent of maximal predicted heart rate but had no angina or ischemic S-T changes.

TABLE 1

Interpretation of Graded Exercise Test

	Achieved 90% of Predicted Heart Rate	1 mm Flat or Downsloping S-T Depression	Angina During Test
Negative test	Yes	No	No
Electrocardiographically positive test	Yes or no	Yes	Yes or no
Clinically positive test	Yes or no	No	Yes
Inconclusive test	No	No	No

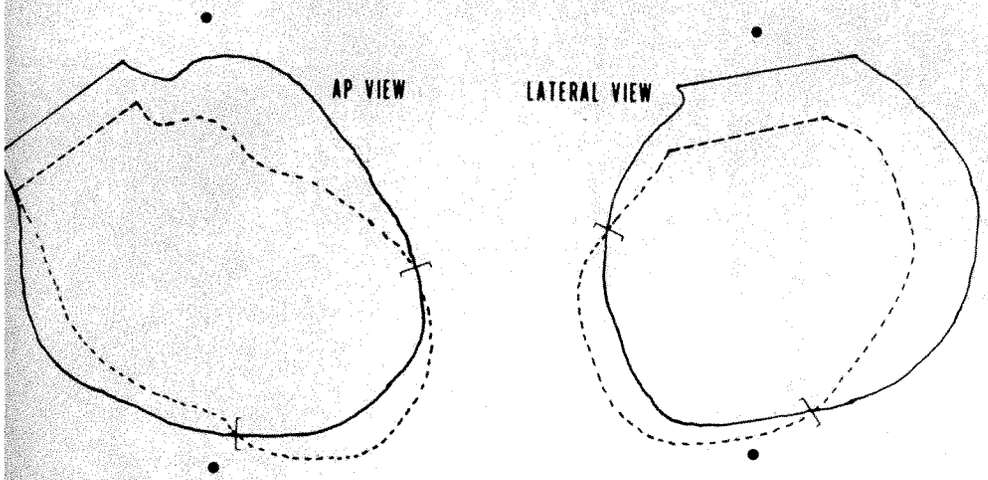
S-T segment elevation (1 mm or more above the baseline value) was documented when it occurred but was not utilized to define an electrocardiographically positive test.

Rate-pressure product (RPP) in mm Hg/min for each patient was calculated as RPP = (HR_{max}) (BP), where HR_{max} is the maximal heart rate achieved during the graded exercise test and BP is the systolic blood pressure in mm Hg at the maximal heart rate.

Cardiac catheterization: Informed consent was obtained and patients were premedicated with 50 mg of Phenergan® and 0.6 mg of atropine administered intramuscularly approximately 30 minutes before catheterization. Cardiac output was measured with the Fick technique,[26] and then each patient underwent biplane large film or cine left ventriculography, and selective coronary arteriography with the Judkins technique.[27] Quantitative angiographic volume measurements were performed using the area-length method of Dodge et al.[28] Angiographic scar size was estimated by determining the percent abnormally contracting segment using the method of Feild et al.[29] (Fig. 1).

The coronary arteriograms were reviewed by two of us and by a cardiac radiologist, and the severity of stenosis was assessed in multiple projections. Vessels judged to have 70 percent or greater narrowing of luminal diameter in any projection were interpreted as having significant stenosis.

The combined coronary and left ventricular angiographic data for each patient were utilized to assess whether the left ventricular myocardium was jeopardized. *Jeopardized* myocardium was defined as normally contracting or hypokinetic tissue supplied by a coronary vessel having 70 percent or greater stenosis. *Nonjeopardized* myocardium was defined as akinetic or dyskinetic tissue. Thus, a patient with single vessel (70 percent or greater) coronary arterial stenosis and an akinetic or dyskinetic zone corresponding to the distribution of the diseased coronary vessel would be categorized as having *nonjeopardized* myocardium. However, a patient with



$$\text{PERCENT ABNORMALLY CONTRACTING SEGMENT} = \frac{\text{AKINETIC or DYSKINETIC LENGTH of END DIASTOLIC CIRCUMFERENCE}}{\text{TOTAL END DIASTOLIC CIRCUMFERENCE}} \times 100$$

FIGURE 1. Angiographic estimation of left ventricular scar size.[28] End-diastolic (**solid lines**) and end-systolic (**dashed lines**) left ventricular silhouettes in anteroposterior (AP) and lateral projections were superimposed using fixed X-ray beam markers (**solid dots**) as references. The portion of the end-diastolic circumference that was akinetic or dyskinetic, shown as the region between the brackets, was expressed as a percent of the total end-diastolic circumference, averaged for the two projections and designated the "percent abnormally contracting segment."

ABLE II

linical Findings In 100 Patients Evaluated After Myocardial farction

	Patients (no.)
Prior myocardial infarct	
1	78
2	18
3	4
ECG	
Location of infarct	
Anterior	48
Inferior	48
Indeterminate	4
LVH	3
Resting S-T elevation	4
Chest pain	
Classic angina	59
Atypical	12
None	29
Severity of exertional angina*	
Class 1	4
Class 2	33
Class 3	22
Class 4	0
Severity of CHF†	
Class I	86
Class II	9
Class III	5
Class IV	0
Medications	
Digoxin	23
Diuretic drugs	19
Propranolol	18
Physical examination	
Rales	1
Ventricular gallop	12
Edema	1
Cardiomegaly	11

* Canadian Cardiovascular Society criteria.[20]
† New York Heart Association criteria.[21]
CHF = congestive heart failure; ECG = electrocardiogram; LVH = ft ventricular hypertrophy.

multivessel coronary artery disease and an isolated akinetic or dyskinetic zone would be classified as having *jeopardized* tissue.

Statistics: Continuous data are reported as mean values ± standard error of the mean. Student's t test was used to assess differences between means of independent observations. The chi-square test was used to assess differences between proportions. Linear correlations were found by the method of least-squares analysis. The predictive value of exercise testing was defined as the ratio of true positive tests to the sum of true positive tests plus false positive tests, expressed as a percent.

Results

Clinical findings: In the study group, there were 93 men and 7 women who ranged in age from 32 to 68 years (mean 48 ± 8 years). The patients were studied a median of 4.5 months (mean 13 ± 2 months) after their most recent infarction. Additional clinical findings are listed in Table II. Fifty-nine patients had typical exertional angina pectoris that had first occurred a median of 2.5 months (mean 6 ± 1 months) before admission. An equal number of patients had anterior and inferior infarction, and only 14 percent of patients had had congestive heart failure. Most of the patients were not taking cardiac medications and had essentially normal findings on the cardiac physical examination.

Graded exercise test: There were no complications during exercise testing. Of the 100 patients, 21 had a negative graded exercise test, 31 an electrocardiographically positive test, 19 a clinically positive test and 29 an inconclusive test (Fig. 2). Table III shows the average values for the duration of exercise, maximal heart rate and rate-pressure product.

Only 3 of the 31 patients (10 percent) with an electrocardiographically positive test were receiving digoxin.

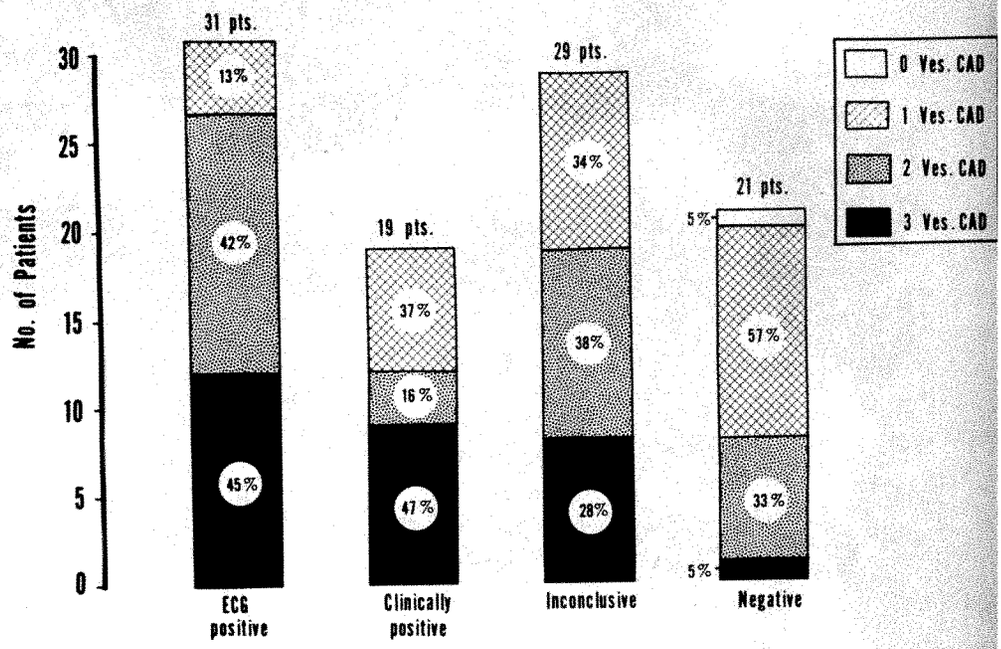


FIGURE 2. Interpretation of graded exercise test in 100 patients (pts.) after infarction. An electrocardiographically (ECG) positive result was highly predictive (87 percent) of multivessel coronary artery disease (CAD). A negative graded exercise test predicted zero or single vessel disease (62 percent) and only rarely occurred in patients with triple vessel disease (5 percent). Clinically positive and inconclusive graded exercise tests were not as helpful in predicting the extent of coronary artery disease. Ves. = vessel.

However, 8 of 29 patients (28 percent) with an inconclusive test were receiving propranolol, thus suggesting that propranolol might significantly alter the graded exercise test response in this population.

Ten patients had transient S-T segment elevation during exercise, and 4 additional patients had a significant (1 mm or greater) increase in the baseline level o S-T segment elevation during the exercise test. Six o 29 patients (21 percent) who had no history of chest pair had an electrocardiographically positive graded exercis test; 5 of these 6 patients did not manifest angina con current with S-T changes during exercise.

The primary indication for termination of exercis in the 100 patients was dyspnea or fatigue, or both (4 percent), followed by angina or ischemic S-T changes or both (37 percent), achievement of target heart rat (11 percent), arrhythmia (7 percent), dizziness (2 per cent) and claudication (2 percent). Of the 37 patient terminating exercise because of angina or S-T depres sion, or both, 13 had S-T depression alone, 6 had angin alone and 18 had both S-T depression and angina.

TABLE III

Graded Exercise Test Performance Related to Extent of Coronary Artery Disease

	Vessels With 70 Percent Stenosis				
	0	1	2	3	Total
Number of patients	1	33	35	31	100
Age (mean) (yr)	39	47 ± 1	48 ± 2	51 ± 2	48 ± 1
Test performance					
Exercise duration (sec)	625	421 ± 24*	345 ± 21	286 ± 25†	355 ± 23
Maximal heart rate (beats/min)	169	152 ± 4*	138 ± 4	133 ± 4†	141 ± 4
Rate-pressure product (mm Hg/sec)	27,040	23,760 ± 950*	20,433 ± 931	20,182 ± 974†	21,519 ± 941
S-T elevation during exercise	1	5	3	5	14
Indication for termination of test					
Chest pain or ischemic S-T changes or both	0	9	11	17	37
Fatigue or dyspnea	0	14	14	13	41
Arrhythmia	0	3	4	0	7
90% of predicted heart rate achieved	0	5	5	1	11
Other	1	2	1	0	4
Medications used before test					
Propranolol	0	3	8	7	18
Digoxin	0	6	8	9	23

* $P < 0.05$ (single vessel versus double vessel disease); † $P < 0.05$ (triple vessel versus single vessel disease); data for double vessel and triple vessel disease were not significantly different.

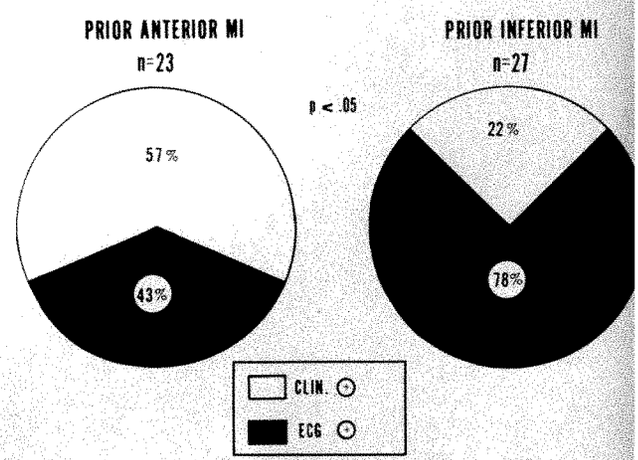


FIGURE 3. Positive graded exercise tests in patients with prior anteri and inferior myocardial infarction. (MI). Of patients with a positive e ercise test, significantly more electrocardiographically (ECG) positiv responses than clinically (CLIN.) positive responses were noted patients with a prior inferior infarction. n = number of patients; p probability.

TABLE IV

ndexes of Left Ventricular Performance Related to Extent f Coronary Artery Disease

	Vessels With 70 Percent Stenosis				
	0	1	2	3	Total
atients (no.)	1	33	35	31	100
ite of infarct					
Anterior	1	18	18	11	48
Inferior	0	15	15	18	48
Indeterminate	0	0	2	2	4
ardiac index (liters/min per m²)	4.0	3.0 ± 0.1	2.8 ± 0.1	3.0 ± 0.1	2.9 ± 0.1
F (%)	33	42 ± 2	42 ± 2*	36 ± 2†	40 ± 1

* $P < 0.05$ (double vessel versus triple vessel disease); † $P < 0.05$ riple vessel versus single vessel disease); data for single vessel and ouble vessel disease were not significantly different.
EF = left ventricular ejection fraction.

Of 27 positive graded exercise tests in patients with rior inferior infarction, 21 (78 percent) were electro-ardiographically positive whereas only 10 (43 percent) f the 23 positive tests in patients with prior anterior ıfarction were electrocardiographically positive (P 0.05) (Fig. 3). Exercise duration did not differ between atients with anterior and inferior infarction (351 ± 20 ersus 362 ± 21 seconds.

Angiographic and hemodynamic studies: Of the 00 patients, 31 had three vessel coronary artery disease 70 percent or greater stenosis), 35 had two vessel dis-ase, 33 had one vessel disease and 1 patient had no essel with 70 percent or greater stenosis. Three patients ad 50 percent or greater stenosis of the left main cor-nary artery.

Indexes of myocardial performance as related to the tent of coronary artery disease are presented in Table 7. The extent of coronary artery disease was similar in atients with prior anterior and inferior infarction. jection fraction was lower in patients with three vessel isease than in those with single or double vessel dis-ase.

Correlation of graded exercise test with coro-ary anatomy and left ventricular hemodynamics: f the 21 patients with negative graded exercise test, 13 2 percent) had zero or single vessel coronary artery sease, and only 1 patient (5 percent) had triple vessel sease (Fig. 2). Twenty-seven of the 31 patients (87 ercent) with an electrocardiographically positive ex-cise test had multivessel coronary artery disease. owever, there was a more even distribution of one, two nd three vessel coronary artery disease among patients aving either a clinically positive or an inconclusive test; us these latter test responses were not helpful in dif-rentiating the number of diseased vessels.

One vessel coronary artery disease was associated ith 50 to 69 percent stenosis of additional vessels in 3 4 patients (75 percent) with an electrocardiographi-lly positive test, 2 of 8 patients (25 percent) with a inically positive test and 3 of 12 patients (25 percent) ith a negative test.

TABLE V

Significance of Jeopardized Myocardium

	Myocardium Jeopardized (no. = 79)	Myocardium Not Jeopardized (no. = 21)	P
Mean age of patient (yr)	49 ± 1	48 ± 2	NS
ECG site of infarct			
Anterior	30	18	<0.001
Inferior	45	3	
Indeterminate	4	0	
Chest pain			
Classic angina	51	8	<0.10
Atypical	7	5	
None	21	8	
Exercise test interpretation			
Negative	12	9	<0.01
Electrocardiographically positive	31	0	
Clinically positive	15	4	
Inconclusive	21	8	
Exercise test performance			
Exercise duration (sec)	344 ± 16	394 ± 31	NS
Maximal heart rate (beats/min)	137 ± 3	150 ± 5	<0.10
Rate-pressure product (mm Hg/sec)	20,894 ± 704	22,767 ± 1043	NS
Vessels with CAD			
0	0	1	<0.001
1	15	18	
2	33	2	
3	31	0	
Ejection fraction (%)	42 ± 1	35 ± 2	<0.02

CAD = coronary artery disease; ECG = electrocardiographic; no. = number of patients; NS = not significant; P = probability.

Six of the 29 patients who gave no history of antecedent angina had an electrocardiographically positive graded exercise test; 5 of these 6 patients were found to have two or three vessel disease. Eleven (38 percent) of the 29 asymptomatic patients had a negative graded exercise test.

The myocardium was considered *jeopardized* in 79 patients and not jeopardized in 21 (Table V). Patients without jeopardized myocardium had a greater prevalence of prior anterior infarction, single vessel (left anterior descending) coronary arterial stenosis and a lower ejection fraction than the patients with jeopardized myocardium. Of the 50 patients with a positive (electrocardiographically or clinically) graded exercise test, 46 (92 percent) were identified as having jeopardized myocardium; no electrocardiographically positive response occurred in patients without jeopardized myocardium. There were no significant differences in duration of exercise or rate-pressure product between the groups with and without jeopardized myocardium.

There was a significant correlation ($r = 0.65$, no. = 41) between ejection fraction and duration of exercise in patients who discontinued exercise because of severe dyspnea or fatigue (symptoms of left ventricular dysfunction) (Fig. 4). Furthermore, in these patients, the angiographic scar size also correlated significantly with duration of exercise ($r = -0.62$, no. = 39).

S-T segment elevation during exercise tended to occur in patients whose ejection fraction was significantly lower and whose angiographic scar was signifi-

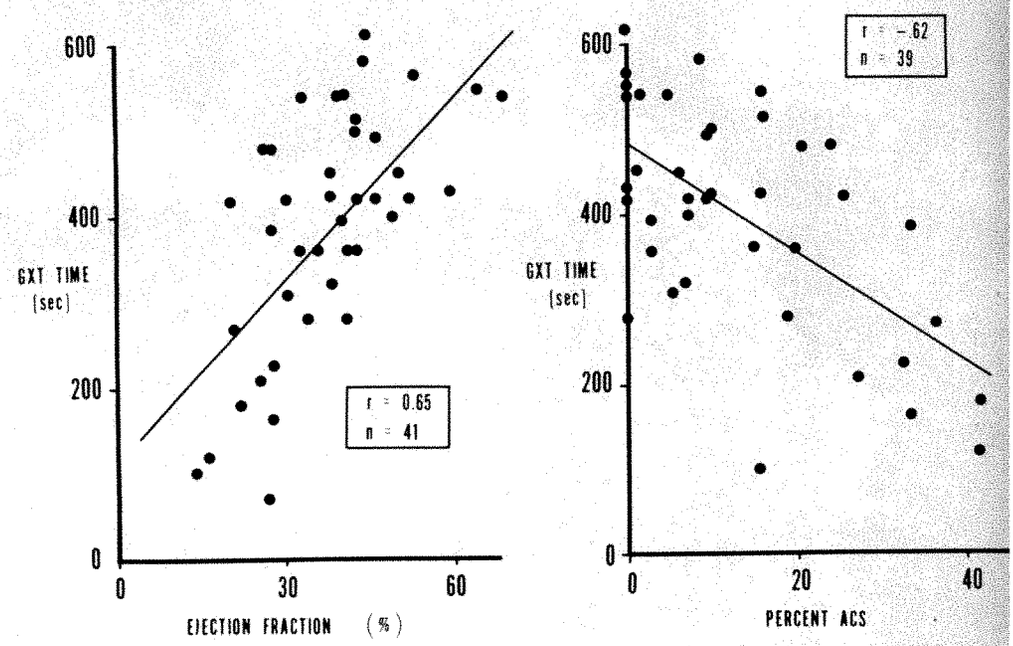


FIGURE 4. Duration of exercise versus left ventricular performance in patients limited by fatigue or dyspnea, or both. Significant correlations (*r*) between graded exercise test (GXT) time and both ejection fraction and angiographic scar size (percent ACS) were noted. n = number of patients.

cantly larger ($P < 0.0001$) than those of the other patients (Fig. 5). Of the 14 patients with S-T elevation during exercise, 13 (93 percent) had 70 percent or greater stenosis of the left anterior descending coronary artery and 12 (86 percent) had a prior anterior myocardial infarction.

Discussion

Our study confirms that the graded exercise test is a safe and helpful screening tool in evaluating the postinfarction patient. An electrocardiographically positive test is highly predictive of multivessel coronary artery disease, and a negative test favors single vessel disease. Exercise-induced S-T segment elevation suggests severe left ventricular asynergy or aneurysm. Duration of exercise in patients limited by fatigue and dyspnea quantitatively reflects left ventricular pump function and scar size.

Sensitivity of exercise testing in postinfarction patients: The graded exercise test is generally thought to have a 65 to 75 percent sensitivity rate in detecting coronary artery disease[13]; however, Ellestad and Wan[14]

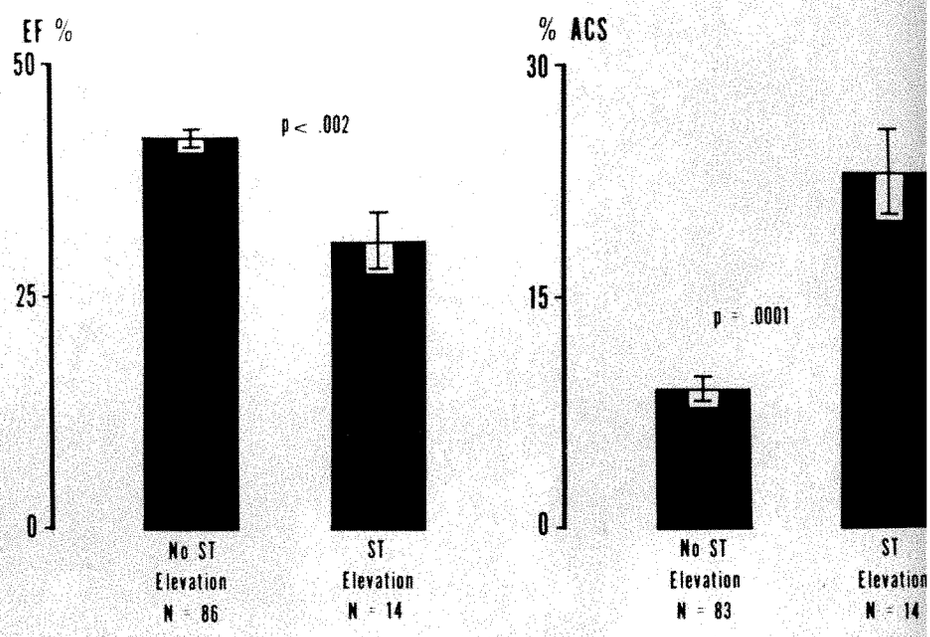


FIGURE 5. Relation of S-T elevation to ejection fraction (EF) and percent abnormally contracting segment (ACS). Patients having S-T segment elevation during exercise had a significantly lower ejection fraction and a larger percent abnormally contracting segment than the remaining patients. N = number of patients; p = probability.

eported a decreased incidence of electrocardiographically positive tests in patients with prior infarction. In ur study of 100 subjects after infarction, 50 patients ad a positive exercise test, and 31 of these had definite schemic electrocardiographic changes. An *electrocardiographically positive* exercise test response tended o occur more frequently in patients with a prior *inferior* nfarction; a *clinically positive* response occurred more requently in patients with a prior *anterior* infarction Fig. 3), although multivessel coronary artery disease vas common in each group (81 percent [17 of 21] in the roup with inferior infarction and 69 percent [9 of 13] n the group with anterior infarction.

As an explanation for these findings, electrocardiographically positive responses might be expected to eflect ischemia not in the zone of prior infarction but n adjacent or opposite zones of viable tissue having ompromised coronary blood flow. Furthermore, as reviously noted,[30] exercise testing might more readily etect ischemia of the anterior than of the inferior wall. hese postulates may thus explain why our patients ith a prior inferior infarction had a greater incidence f electrocardiographically positive exercise responses an those with a prior anterior infarction. A recent udy involving only patients with prior inferior inarctions[31] supports this theory: An electrocardiographically positive exercise test occurred in 37 of 52 patients [71 percent], and 32 (86 percent) of these 37 patients had multivessel coronary artery disease.

Exercise testing to predict extent of coronary rtery disease: In our study, 21 patients had a false egative exercise test, a finding related to the lesser xtent of coronary artery disease in these patients.[13] hirteen of our 21 patients (62 percent) with a negative xercise test had zero or single vessel coronary artery isease, whereas only one patient with a negative excise test had three vessel disease.

An electrocardiographically positive exercise test ter infarction in our series was highly predictive (87 rcent) of multivessel disease. Miller et al.,[31] studying atients with prior inferior infarction, similarly found at 78 percent of their subjects with electrocardiraphically positive exercise tests had multivessel ronary artery disease. The finding of a positive exerse test in patients after infarction may be of great ognostic significance because, as shown by Ellestad d Wan,[16] the likelihood of having a new coronary ent (progession of angina, myocardial infarction or ath) is twice as great in these patients as in positive sponders who have not experienced a previous inrction.

Furthermore, our results indicate that an electrordiographically positive exercise test in an *asymptmatic* patient is an especially sensitive indicator of vere coronary artery disease. We found an 83 percent of 6) incidence rate of multivessel disease in our ymptomatic postinfarction patients who had an ectrocardiographically positive exercise test. Sanarco et al.[32] similarly found a high (73 percent) incince rate of three vessel disease in asymptomatic stinfarction patients with a positive exercise test.

Electrocardiographically positive exercise tests in our study also identified patients with jeopardized myocardium—normally contracting or hypokinetic myocardium in the zone of distribution of a coronary artery with 70 percent or greater stenosis. Patients with jeopardized myocardium also tended to have more extensive coronary artery disease and a higher ejection fraction than patients lacking jeopardized myocardium.

Correlation of left ventricular pump function with scar size: The availability of quantitative angiographic volume and scar size measurements in this series provided an opportunity to correlate graded exercise test performance with left ventricular pump performance and scar size. Such correlations would be expected to occur primarily in patients limited by symptoms of left ventricular failure (for example, dyspnea or fatigue) rather than by signs or symptoms of ischemia (chest pain or S-T changes). There was a surprising correlation ($r = 0.65$) between left ventricular ejection fraction and exercise duration in patients whose exercise test was limited by dyspnea or fatigue. Interestingly, all patients exercising 200 seconds or less had an ejection fraction of 30 percent or less. Similarly, in these patients, a good inverse correlation ($r = -0.62$) was found between angiographic scar size, as expressed by percent abnormally contracting segment, and duration of exercise. These significant correlations between exercise duration and both left ventricular pump function and angiographic scar size suggest that the exercise test in selected patients might indeed provide insight into left ventricular performance and scar size.

Exercise-induced S-T elevation: The occurrence of S-T elevation during exercise was not considered a positive criterion for ischemia in our series, but rather an indication of abnormal left ventricular wall motion. We observed 14 patients with S-T elevation during exercise, and the angiographic scar size was strikingly greater and the ejection fraction significantly more diminished than in patients without S-T elevation during exercise.

In these patients with S-T elevation during exercise, there was a predominance of severe left anterior descending coronary artery disease. Twelve of the 14 patients had had a prior anterior infarction. Thus our data quantitatively establish that S-T elevation during exercise is associated with a large zone of left ventricular asynergy. These observations are in accord with those of others[33–35] who found a significant correlation between exercise-induced S-T elevation and left ventricular aneurysm.

Clinical implications: This study documents that the graded exercise test is a safe diagnostic tool in the primary evaluation of patients after myocardial infarction. Such patients can undergo exercise testing within several months of infarction to determine functional capacity, presence of exertional angina and the possible need for coronary arteriography as well as the consideration for coronary revascularization surgery.

The categorization of the graded exercise test responses as negative, positive and inconclusive allows a relatively accurate prediction of the extent of coronary

artery disease and the degree of left ventricular dysfunction in certain patient subgroups. The negative graded exercise test predicts zero or single vessel coronary artery disease with a predictive value of 62 percent. An electrocardiographically positive graded exercise test, more common after inferior than after anterior myocardial infarction, predicts multivessel coronary artery disease with a predictive value of 87 percent.

Clinically positive and inconclusive exercise test results are not helpful in predicting the extent of coronary artery disease; however, in patients who are limited by dyspnea or severe fatigue during exercise, exercise duration correlates with degree of left ventricular dysfunction assessed angiographically. The correlation of S-T elevation during exercise with a large angiographic scar and a reduced ejection fraction is also of diagnostic significance.

Acknowledgment

We gratefully acknowledge the secretarial assistance of Dana Murray in the preparation of this manuscript.

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Correlation of Electrocardiographic and Pathologic Findings in Healed Myocardial Infarction

WILLIAM SULLIVAN, BA
STEVEV VLODAVER, MD, FACC
SALVATORE TUNA, MD, FACC
LINDA LONG, MD
JESSE E. EDWARDS, MD, FACC

St. Paul and Minneapolis, Minnesota

A correlative study in 50 cases of healed myocardial infarction compared the 12 lead electrocardiogram with pathologic observations. The electrocardiogram was interpreted according to established Minnesota codes with some modifications. The following conclusions were reached: (1) The electrocardiogram underestimates the extent of myocardial infarction. (2) When a healed myocardial infarct at a specific location is recognized with electrocardiographic criteria, it is likely that there are unrecognized infarcts involving other areas of the left ventricle. (3) Infarctions involving the lateral and inferobasal areas are frequently unrecognized. (4) The electrocardiogram is more likely to miss myocardial infarcts in patients with multiple, than in those with single, electrocardiographically diagnosed infarcts. (5) Apical myocardial infarction does not appear to have specific electrocardiographic findings, other than those related to general infarct localization by electrocardiogram, particularly in patients with anteroseptal or anterolateral infarction. (6) Abnormal Q waves, generally thought to indicate transmural myocardial infarction, are frequently found in subendocardial infarction. (7) The simplified electrocardiographic classification of myocardial infarct site (anteroseptal, inferior, anterolateral) used in this study is preferable to more detailed classifications previously suggested by others.

Most reports correlating electrocardiographic and pathologic findings in acute myocardial infarction agree that the electrocardiographic diagnosis is commonly correct.[1] However, the electrocardiogram is generally considered less precise[2] in the diagnosis and localization of healed myocardial infarction. Levine and Phillips,[3] using the Wilson criteria for diagnosis of healed myocardial infarction, found in a study of 23 cases that only 20 percent of healed infarcts observed at autopsy were revealed in the electrocardiogram. In a correlative study of electrocardiographic and autopsy findings, Wood et al.[4] adopted the 1959 criteria of the World Health Organization Expert Committee on Cardiovascular Diseases and Hypertension for "very probable myocardial infarction." Among 122 cases, they found that the accuracy rate of electrocardiographic diagnosis was 82 percent in acute infarction but only 27 percent when there was a single healed infarct. When multiple sites of old infarction were present, the accuracy rate increased to 58 percent, but the overall accuracy rate was only 48 percent.

The purpose of this study was to correlate in 50 cases of healed myocardial infarction the anatomic and electrocardiographic findings, interpreted with use of Minnesota Q and QS codes.

Material and Methods

Fifty consecutive patients with an autopsy-demonstrated healed myocardial infarct and at least one 12 lead electrocardiogram taken within 21 days of death were studied. Ten of the 50 patients had an acute myocardial infarction in addition to the healed infarct. Thirty-three patients were men and 17 were women. The age range was 32 to 89 years.

om the Department of Pathology, United Hos-
als-Miller Division, St. Paul, Minnesota and the
partments of Pathology and Medicine, Univer-
y of Minnesota, Minneapolis, Minnesota.

This
dy was supported by Public Health Service
search Grant 5 RO1 HL 05694 from the National
art, Lung, and Blood Institute, National Institutes
Health, Bethesda, Maryland, and by the Saint
ul Foundation, St. Paul, Minnesota. Manuscript
ceived May 25, 1978; revised manuscript re-
ived June 27, 1978, accepted June 28, 1978.

Address for reprints: Jesse E. Edwards, MD,
ited Hospitals-Miller Division, Department of
thology, 125 West College Avenue, St. Paul,
nnesota 55102.

Pathologic Examination

At the time of autopsy, the heart specimens had been sectioned into five horizontal slices of approximately equal thickness from apex to base, each section measuring 0.8 to 1.3 cm in thickness. They were fixed in formaldehyde. By gross examination, the sites of infarction were indicated on diagrams of cross sections of the ventricles. Slice 1 was apical and slice 5 was basal. Histologic examination was performed on at least three portions of the left ventricle, each representing distribution of each of the three main coronary arteries.

Each myocardial infarct, whether acute or healed, was classified as subendocardial or transmural. All infarcts were further classified according to their location in the heart as a whole:

Pathologic identification of sites of infarction: *Anterobasal* (anterior wall, including the anterior half of anterolateral papillary muscle—may include septum)—slices 4 and 5; *anteroseptal* (anterior wall and septum)—slices 1 to 3; *anterolateral* (anteroseptal and lateral)—slices 1 to 4; *lateral* (between the anterior edge of the posteromedial papillary muscle and the middle of the anterolateral papillary muscle)—slices 2 to 4; *apical**—slices 1 and 2; *inferior* (involving the ventricular septum and inferior wall including the posteromedial papillary muscle)—slices 2 to 4; *inferobasal*—defined as inferior but restricted to slices 4 and 5; *septal* (strictly septal)—slices 2 to 4; *inferolateral* (confluence of inferior and lateral areas)—slices 2 to 4; *inferolateral basal* (confluence of lateral and inferobasal areas)—slices 4 and 5.

In Table I, infarcts are further classified according to amount and type of wall involved: transmural acute (TA); transmural healed (TH); subendocardial extensive acute (EA); subendocardial extensive healed (EH); subendocardial limited acute (ea); and subendocardial limited healed (eh).

Electrocardiographic Definitions

Serial 12 lead electrocardiograms were reviewed and the diagnosis of healed myocardial infarction was made when Minnesota Q or QS codes (1-1, 1-2 and 1-3) were present[5] and there were no ST-T changes of acute myocardial infarction. When ST-T changes were present without diagnostic Q or QS codes, these were indicated as signs of either ischemia or acute infarction.

Location of healed myocardial infarction: The electrocardiographic localization of healed myocardial infarcts was made according to the following criteria[6]: *Anteroseptal*—Q, QS codes in leads V_1 to V_5; *Anterolateral*—Q, QS codes in leads I, aVL and V_6; *Inferior*—Q, QS codes in leads II, III and aVF.

Of the anatomic locations given, the Minnesota codes are defined only for anteroseptal, anterolateral and inferior healed myocardial infarction. We added an electrocardiographic diagnosis of inferobasal myocardial infarction and also criteria for the diagnosis of healed myocardial infarction in the presence of "atypical left bundle branch block." In the absence of either right bundle branch block or right ventricular hypertrophy, the electrocardiographic diagnosis of inferobasal healed infarction was based on an R/S ratio in lead V_2 greater than 1, absence of a Q wave in lead V_2 and an R wave duration in lead V_2 of 0.4 second or greater. A diagnosis of myocardial infarction was also considered in the presence of "atypical left bundle branch block" when abnormal Q waves were present or abnormal Q or Q-equivalent (M-shaped or rsR′) waves were present in leads I, aVL, V_5 or V_6.[7] A QRS duration of 0.09 second or less was considered normal, and individual values were not indicated separately in the table. A QRS duration of 0.10 second or greater was indicated individually in each case. Intraventricular conduction delay was diagnosed when the QRS duration was 0.11 second or greater.

"Abnormal" Q waves in leads V_5 and V_6: To correlate Q waves in leads V_5 and V_6 with apical involvement, the Q wave in lead V_5 was arbitrarily called "abnormal" when it had a minimal duration of 0.02 second and a Q/R amplitude ratio of at least 0.05. In 16 of 50 patients there was an abnormal Q wave in lead V_5, the mean Q duration being 0.03 second (range 0.02 to 0.06) and the mean Q/R amplitude ratio 0.19 (range 0.04 to 0.5).

An "abnormal" Q wave in lead V_6 was arbitrarily diagnosed when the Q wave duration was at least 0.02 second and the Q/R amplitude ratio was at least 0.053. In 17 patients with an abnormal Q wave in lead V_6, the mean Q wave duration was 0.036 second (range 0.02 to 0.05) and the mean Q/R amplitude ratio was 0.173 (range 0.053 to 0.33). In 13 patients with a "normal" Q wave in lead V_5 the mean Q wave duration was 0.015 second (range 0.01 to 0.02), whereas in 13 patients with a "normal" Q wave in lead V_6 the mean duration was 0.016 second (range 0.01 to 0.02). The mean Q/R amplitude ratio in patients with a "normal" Q wave was 0.037 (range 0.004 to 0.091), and 0.06 (range 0.005 to 0.111) for leads V_5 and V_6, respectively.

Ischemia or subendocardial myocardial infarction: A diagnosis of ischemia or acute subendocardial myocardial infarction was considered when Q or QS code criteria were absent and there was horizontal S-T depression of 2 mm or greater or "ischemic T wave inversions" of 5 mm or more with or without S-T segment shifts in the absence of (1) electrolyte abnormalities, (2) left ventricular hypertrophy with strain, (3) intraventricular conduction abnormalities, (4) intracranial disease, or (5) digitalis, quinidine or procainamide administration. The diagnosis of electrocardiographic abnormalities other than myocardial infarction was made according to New York Heart Association criteria.[8]

The electrocardiograms were first read for diagnosis of specific areas of infarction; then the diagnosis was compared with the pathologic findings. Table I is averaged according to the various electrocardiographic diagnoses, listing the pathologic findings within each diagnostic category.

Results

General Observations

Multiple sites of healed infarction were common. Six patients had one healed infarct, 18 had two healed infarcts, 19 had three healed infarcts and 7 had four or more separate sites of healed infarction. Ten of the 50 patients had an acute or healing infarct in addition to one or more healed infarcts. The healed myocardial infarcts were of the following types: transmural only (10 patients); subendocardial only (23 patients); and transmural and subendocardial (17 patients).

In order of decreasing frequency, the sites of healed myocardial infarction were anteroseptal (17), apical (16), inferobasal (15), inferior (11), anterolateral (11), lateral (3), anterobasal (3) and septal (2). There was apical involvement in 33 percent of patients (2 of 6) with a single infarct, in 78 percent of patients (14 of 18) with

* Apical infarction may be anterior, lateral, inferior or circumferential. As indicated, the apical segment may be part of a larger segment, such as anteroseptal or inferior; in such cases, apical involvement will not be mentioned separately. If apical involvement is in one or more areas other than that of the "large segment," then it is indicated separately (for example, anteroseptal and apical lateral). In identifying sites of infarction, the majority rule was always applied (if slices 4 and 5 were involved but the lesion included part of slice 3, the final diagnosis was anterobasal).

two areas involved, in 89 percent of patients (17 of 19) with three areas involved and in 100 percent of patients (7 of 7) with four or more sites involved.

Correlations of Electrocardiographic and Pathologic Findings

The sections under this heading indicate the electrocardiographic categorization of each case by location of infarction. These findings are listed, related to the pathologic findings and discussed in relation to a particular electrocardiographic grouping.

Inferior infarction (six cases, Table IA): Among the six patients with an electrocardiographic diagnosis of healed infarction restricted to the inferior wall, the pathologic examination confirmed this finding in only one. In two other patients, although the inferior wall was involved, there was additional involvement (inferobasal

TABLE I

Electrocardiographic and Pathologic Findings in 50 Cases of Healed Myocardial Infarction

Case no.	Age (yr) & Sex	Minn. Code	Associated Electrocardiographic Findings	QRS Duration (seconds)	Q Wave in V_5–V_6	Heart Weight (g)	Myocardial Infarction		Apex Involved
							ECG Confirmed	Other	
A. Inferior Myocardial Infarction by Electrocardiogram (6 cases)									
1	53 M	1-1-4	LVH, LAD	Normal	Abnormal	650	No	Apical circumferential EH; anterolateral EH; inferolateral basal TH	Yes
2	58 M	1-1-4	. . .	Normal	Abnormal	560	Yes, eh	None	Yes
3	72 M	1-1-4	LVH with strain, ST-T changes	Normal	Normal	560	Yes, TH	Inferobasal TH; lateral ea	No
4	56 F	1-1-4	Anterior ischemia or subendocardial infarction	Normal	Normal	350	Yes, EH	Anteroseptal EH; inferobasal EH	Yes
5	50 M	1-2-4	Anterolateral ischemia?	Normal	Normal	570	No	Lateral EH	No
6	88 M	1-1-4	IVCD, LVH, LAD	0.11	No Q	400	No	Apical circumferential EH; anterolateral EH; inferolateral basal TH	Yes
B. Inferior and Inferobasal Myocardial Infarction by Electrocardiogram (3 cases)									
7	63 F	1-1-4	. . .	Normal	Abnormal	380	Yes, TH	Lateral TH	No
8	81 F	1-1-4	LVH with strain	Normal	Normal	500	Yes, TH	Lateral TH; apical circumferential EH	Yes
9	61 M	1-2-4	. . .	Normal	Normal	340	No, inferior; yes, inferobasal	eh	No
C. Inferobasal Myocardial Infarction by Electrocardiogram (1 case)									
10	70 M	. . .	. . .	Normal	No Q	450	Yes, EH	None	No
D. Anteroseptal Myocardial Infarction by Electrocardiogram (10 cases)									
11	73 M	1-2-8	. . .	Normal	Normal	510	Yes, EH	Apical anterior ea; apical circumferential eh; inferobasal eh	Yes
12	72 F	1-1-2	LVH with strain	Normal	Normal	500	Yes, eh	Inferobasal eh	Yes
13	65 M	1-1-1	IVCD, lateral ischemia or subendocardial MI	0.11	Abnormal in V_5; no Q in V_6	370	Yes, EA	Inferior eh	Yes
14	72 M	1-1-7	LVH, LAD, 1° A-V block	0.10	No Q in V_6	550	Yes, EH	Anterolateral EH; inferolateral EH; inferolateral basal EH	Yes
15	80 M	1-3-1	IVCD (atypical LBBB), 1° A-V block	0.14	No Q	480	Yes, eh	Anterobasal eh	No
16	80 F	1-2-8	Anterolateral ischemia or subendocardial MI, 1° A-V block	Normal	No Q	560	Yes, EA, EH	Inferolateral EA; anterolateral EH	Yes
17	66 M	1-1-1	LVH with strain	Normal	No Q	450	Yes, eh	Lateral eh	Yes
18	75 F	1-2-8	LVH with strain	Normal	Normal	460	Yes, EH	Inferobasal eh; anterolateral EH	Yes
19	32 F	1-2-8	LVH	Normal	Normal	320	Yes, TH	Apical anterolateral TH; apical inferolateral ea	Yes
20	60 F	1-2-8	IVCD, marked LAD	0.11	No Q	495	Yes, TH	Inferobasal EH	Yes
E. Inferior and Anteroseptal Myocardial Infarction by Electrocardiogram (11 cases)									
21	66 M	1-2-4; 1-2-8	Atrial fibrillation, nonspecific ST-T changes	0.10	No Q	500	Yes, anteroseptal TH; No, inferior	Inferobasal TA; anterobasal TH	Yes

TABLE I (continued)

Case no.	Age (yr) & Sex	Minn. Code	Associated Electrocardiographic Findings	QRS Duration (seconds)	Q Wave in V_5-V_6	Heart Weight (g)	Myocardial Infarction		Apex Involved
							ECG Confirmed	Other	
22	59 M	1-1-1; 1-1-2	. . .	Normal	Abnormal	570	Yes, TH	. . .	Yes
23	70 M	1-1-4; 1-2-7	IVCD	0.11	Normal	430	Yes, TH	Anterobasal TH; lateral EH	Yes
24	46 M	1-2-4; 1-2-7	. . .	Normal	Abnormal	480	Yes, anteroseptal EH; no, inferior	Inferobasal TH; inferolateral basal TA	Yes
25	73 M	1-1-4; 1-2-8	IVCD, PVCs, atrial fibrillation	0.11	Abnormal	810	Yes, anteroseptal TH; inferior EH	Anterobasal TH; inferolateral basal EH	Yes
26	45 M	1-1-4; 1-1-7	IVCD	0.11	Abnormal in V_6	330	Yes, EH	Apical circumferential EA	Yes
27	75 F	1-1-4; 1-2-8	LVH	Normal	No Q	400	Yes, EH	Apical inferolateral EH; inferolateral basal EH	Yes
28	73 F	1-1-4; 1-2-8	PVCs, LVH, LAD	Normal	No Q in V_6	450	Yes, EH	Inferobasal EH	Yes
29	52 M	1-2-4; 1-1-1	. . .	0.10	Abnormal	360	Yes, inferior eh; anteroseptal TH	None	Yes
30	81 M	1-1-4; 1-2-8	. . .	Normal	No Q	350	Yes, eh	Inferobasal eh; anterolateral eh	Yes
31	55 F	1-2-5; 1-2-8	. . .	Normal	Normal	340	Yes, inferior eh; anteroseptal EH	None	Yes
F. Anterolateral Myocardial Infarction by Electrocardiogram (6 cases)									
32	59 M	1-1-1	Atypical LBBB	0.14	Abnormal	510	Yes, EH	Inferolateral EH	Yes
33	63 M	. . .	Atypical LBBB	0.14	No Q	460	Yes, TH; EA	Anterobasal EH; inferobasal eh	Yes
34	64 M	1-1-2	IVCD (atypical LBBB), LAD, PVCs	0.15	Abnormal	508	Yes, anterior TH; no, lateral	Inferior TH	Yes
35	59 F	1-1-2	RBBB	0.12	Abnormal	320	Yes, lateral EH; no, anterior	Inferolateral EH, inferolateral basal EH	No
36	79 F	1-1-2	. . .	0.10	Abnormal	450	Yes, eh	Inferobasal eh	Yes
37	68 M	1-1-3	LBBB, LAD, PVCs, 1° A-V block	0.14	No Q	500	Yes, EH	Inferolateral EH	Yes
G. Anteroseptal and Anterolateral Myocardial Infarction by Electrocardiogram (7 cases)									
38	86 M	1-1-2; 1-1-2	IVCD	0.12	Abnormal	340	Yes, lateral TH; no, anteroseptal	Inferolateral TH; inferolateral basal TH	Yes
39	79 M	1-1-6; 1-1-2	. . .	Normal	Abnormal in V_5; normal in V_6	520	Yes, TH	None	Yes
40	59 F	1-1-2; 1-1-2	. . .	Normal	Abnormal	610	Yes, anteroseptal TH; no, lateral	Inferobasal EH; inferior EH	Yes
41	60 M	1-1-2; 1-1-1	RBBB	0.13	QS in V_6	540	Yes, lateral TH; no, anterior	Inferolateral TH; inferolateral basal TH	Yes
42	64 F	1-2-8; 1-1-3	IVCD, LVH, atrial fibrillation	0.12	Abnormal in V_6	590	Yes, lateral TH; no, anterior	None	Yes
43	70 M	1-2-8; 1-1-1	Left anterior hemiblock	Normal	Abnormal	490	Yes, anteroseptal TH; no, lateral	Inferior eh	Yes
44	71 M	1-2-8	Atypical LBBB	0.14	No Q	600	Yes, lateral eh; Yes, anterior TH	None	Yes
H. Inferior and Anterolateral Myocardial Infarction by Electrocardiogram (3 cases)									
45	57 M	1-1-1; 1-1-1	IVCD (atypical LBBB)	0.14	Abnormal in V_6	500	Yes, TH	Inferobasal TH	Yes
46	89 M	1-1-4; 1-1-1	RBBB, LVH, 1° A-V block (P-R 0.52)	0.12	Abnormal	720	Yes, lateral, EH; no, inferior	Inferobasal TH	No
47	75 F	1-1-4; 1-1-2	IVCD (atypical LBBB)	0.14	Abnormal	700	Yes, anterolateral EH; no, inferior	Inferobasal TH	Yes
I. Infarction Not Identified by Electrocardiogram (3 cases)									
48	76 M	. . .	Nonspecific ST-T changes in inferior and anterolateral leads (II, III, aVF, V_4–V_6)	Normal	Normal	410	No	Anteroseptal eh; apical inferior eh; inferobasal ea	Yes
49	60 F	. . .	LVH with strain, ischemic T (I, II, V_4–V_6)	Normal	Normal	360	No	Inferior EH; septal EH; inferobasal EH	No
50	70 M	. . .	Nonspecific ST-T changes	Normal	No Q	490	No	Inferobasal eh	No

A-V = atrioventricular; EA = subendocardial, extensive acute infarct; ea = subendocardial, limited acute infarct; ECG = electrocardiogram; EH = subendocardial, extensive healed infarct; eh = subendocardial, limited healed infarct; IVCD = intraventricular conduction defect; LAD = left axis deviation; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; PVCs = premature ventricular complexes; RBBB = right bundle branch block; TA = transmural acute infarct; TH = transmural healed infarct.

and lateral in one and inferobasal and anteroseptal in the other). In the remaining three cases, the inferior region was not involved. In two of these, healed infarction involved the apical, inferolateral basal and the anterolateral regions. In the last case, only the lateral wall was involved.

Comment: The pathologic finding of inferobasal or lateral involvement, or both, in light of the electrocardiographic finding indicating restriction to the inferior regions suggests that the electrocardiographic criteria for inferior infarction are too restrictive. These criteria may be shared by either basal involvement of the diaphragmatic aspect or by the lateral wall. It is possible that the apical circumferential involvement in two cases affected the electrocardiographic diagnosis of inferior wall myocardial infarction. The lack of identification of anterior involvement may be caused by dominance of involvement of one wall negating signs of involvement of the opposite wall.

Inferior and inferobasal infarction (four cases, Table I, B and C): In three patients (Table IB), the electrocardiographic diagnosis was coexistent inferior and inferobasal healed myocardial infarction. This was confirmed at autopsy in two, but in both, lateral involvement evident in the pathologic studies had not been suspected from the electrocardiogram. In the third case, only the inferobasal aspect was involved; the inferior aspect, as defined, was devoid of lesions. In a fourth case (Table IC) the electrocardiographic diagnosis of inferobasal healed myocardial infarction was confirmed.

Comment: The main point of disagreement between the autopsy and electrocardiographic findings was that involvement of the lateral wall by transmural infarction was not suspected when present. This finding may reflect either stronger forces related to the inferobasal lesion or a general tendency for lateral involvement to be relatively silent. The findings also indicate that the electrocardiogram may identify a lesion of the diaphragmatic aspect but lacks specificity in distinguishing the basal from the more apical aspect of this wall.

Anteroseptal infarction (10 cases, Table ID): The electrocardiographic diagnosis of anteroseptal myocardial infarction was confirmed pathologically in all 10 cases. However, the involvement was more extensive than suggested by the electrocardiogram. The most common infarct sites that were not detected were lateral and inferior. With one exception, the lateral and inferior healed infarcts were subendocardial in distribution. The exception involved a transmural apical anterolateral infarct.

Comment: The electrocardiographic criteria for anteroseptal infarction appear to be reliable but in the presence of such infarction signs of other infarcted areas tend to be less dominant and may not be apparent. All but one of the nondiagnosed infarcts were subendocardial; it is not known whether these infarcts would have been apparent if they had been transmural. The one unidentified transmural infarct occupied an anterolateral position.

Inferior and anteroseptal infarction (11 cases, Table IE): The electrocardiographic diagnosis of inferior and anteroseptal infarction was confirmed in 9 of 11 cases. In two cases pathologic study revealed an inferobasal rather than an inferior infarct. In four cases, an inferobasal infarct was present in addition to the confirmed inferior infarct. In 5 of the 11 cases, some involvement of the lateral wall was present pathologically although not identified from the electrocardiogram.

Comment: The observations indicate that anteroseptal infarction is reliably diagnosed with the electrocardiogram and that, in contrast to the immediately preceding cases, coinfarction of the anterior and inferior walls may be identified in some cases. The electrocardiographic criteria for distinguishing inferior from inferobasal infarction are clearly not reliable, and lateral infarction tends to be undetected with the electrocardiogram.

Anterolateral infarction (six cases, Table IF): The electrocardiographic diagnosis of anterolateral myocardial infarction was made in six cases and confirmed in four. In one of the two remaining cases the lateral wall was not involved; in the other the anterior wall was not involved. In each of the six cases additional involvement of either the inferior or the inferobasal aspect was not detected with the electrocardiogram. In one of the latter cases, the nonidentified infarct was inferior and transmural. The diagnosed anterolateral infarct was also transmural.

Comment: The pattern of correlation in this subset conforms to that observed with anteroseptal myocardial infarction and probably indicates that the electrocardiogram responds to a resolution of forces in which the signs of involvement of the anterior wall dominate those of involvement of other sites. In all but one case, there was intraventricular conduction delay (right bundle branch block in one and atypical left bundle branch block in four). All four patients with atypical left bundle branch block had three or more sites involved by healed infarction.

Anteroseptal and anterolateral infarction (seven cases, Table IG): In seven cases, the electrocardiogram indicated both anteroseptal and anterolateral involvement; pathologic findings substantiated this combination in only two cases. In the five remaining cases there was some involvement in the broad zone covered, but the pathologic process was less extensive than suggested by the electrocardiogram. In three of these cases the infarction was primarily lateral and in two primarily anteroseptal. Four specimens showed additional involvement of the inferior or inferobasal walls that was not suggested in the electrocardiogram. Two of these infarcts were transmural.

Comment: Failure of the electrocardiogram to identify a lesion in the inferior wall when there are lesions in some other part of the free wall of the left ventricle was observed in other subsets of this study. The lack of clear correlation with pathologic findings when the electrocardiogram indicates both anteroseptal and an-

terolateral involvement suggests that the electrocardiographic criteria for distinguishing the anterior from the lateral wall are too rigid. Intraventricular conduction delay occurred in four cases.

Inferior and anterolateral infarction (three cases, Table IH): The electrocardiographic diagnosis of inferior and anterolateral infarction was confirmed at autopsy in one case. In the other two cases the inferobasal aspect rather than the inferior region was involved. Additionally, in the one case with pathologic confirmation inferobasal infarction was also present.

Comment: Involvement of the lateral wall does not mask signs of infarction of the diaphragmatic aspect of the left ventricle but, as in previous cases, the electrocardiographic criteria for distinction between the inferior and inferobasal aspects as defined are not reliable.

Nonspecific changes (Table II): In three cases, the electrocardiogram was abnormal but did not indicate a specific zone of infarction. The healed infarction was limited and subendocardial in two cases, anteroseptal in one and inferobasal in the other. In the third case there was extensive subendocardial infarction in the inferior, inferobasal and septal regions.

Comment: The finding that only 3 of 50 cases of pathologically identified healed infarction had a nondiagnostic electrocardiogram suggests that the electrocardiogram is fairly reliable in identifying old infarction whatever its shortcomings are in identifying all specific areas of infarction.

Apical infarction: Of 13 patients with anteroseptal or anterolateral myocardial infarction, or both, and apical circumferential infarction, 3 had left bundle branch block. Two of these had abnormal Q waves. Of the remaining 10, only 3 had "abnormal" Q waves, 3 had no Q wave and 4 had "normal" Q waves. Two subjects, each with a single infarct and apical involvement, had "abnormal" Q waves in leads V_5 and V_6. Of 14 patients with an infarct in two areas and also apical involvement, 9 (64 percent) had an "abnormal" Q wave in leads V_5 and V_6. Of 17 patients with apical involvement and infarction in three areas, 24 percent (4 of 17) showed "abnormal" Q waves in leads V_5 and V_6, whereas of 7 patients with apical involvement and infarction in four areas, 29 percent (2 of 7) had "abnormal" Q waves in these leads. The Q wave was absent in leads V_5 and V_6 in 14 percent of patients (2 of 14) with apical involvement and two areas of infarction, in 41 percent of patients (7 of 17) with apical involvement and three areas of infarction and in 43 percent of patients (3 of 7) with apical involvement and four areas of infarction. Thus, 45 percent of 40 patients (18 of 40) with apical involvement showed "abnormal" Q waves in leads V_5 and V_6, 25 percent (10 of 40) had normal Q waves in these leads and 30 percent (12 of 40) had no Q wave in these leads.

Discussion

General considerations: Numerous studies have correlated electrocardiographic and pathologic findings in instances of healed myocardial infarction.[9–27] The methods used to evaluate the electrocardiograms and pathologic specimens have varied considerably. The electrocardiographic diagnosis of myocardial infarction has been based on abnormal Q waves defined as either a deep Q (Q/R amplitude ratio greater than 25 percent)[28] or a Q wave duration greater than 0.03 or 0.04 second[7,13–19,26,29] or the combination of a Q/R ratio greater than 25 percent and a Q wave duration from onset to nadir greater than 0.02 or 0.03 second, depending on the lead.[13–19] We have used the Minnesota codes in interpreting the 12 lead electrocardiograms. These codes have been used extensively in large scale epidemiologic studies for the diagnosis and localization of myocardial infarction. They include a spectrum of electrocardiographic abnormalities based on degrees of Q wave duration and Q/R amplitude ratio in various leads and provide criteria for myocardial infarction that range from strong (codes 1-1) to somewhat weak (codes 1-3).

The pathologic approaches to examination of the heart also vary considerably. The studies based on multiple gross cross sections of the ventricles generally provide accurate information about the extent and location of myocardial infarcts. Recently, attempts have been made to quantitate the size of myocardial infarcts by subjecting the margins of infarcts to planimetry after obtaining photographs of sections of the heart.[27]

Inferior and inferobasal infarction: Our correlative findings concerning inferior and inferobasal myocardial infarcts diagnosed with the electrocardiogram are in general agreement with those of others.[17,18,25–27] When the electrocardiographic diagnosis is inferior myocardial infarction, the pathologic specimen often shows involvement of the inferobasal and adjacent lateral sites in addition. There is also frequent apical involvement. Our findings suggest that the terms inferior, diaphragmatic and inferoposterior (posterobasal, strictly posterior) are too restrictive, because they imply that the electrocardiogram can distinguish between involvement of one of these areas and involvement of other areas. No electrocardiographic findings were identified in this study that would aid in recognizing involvement of inferobasal, apical and adjacent lateral sites when they are associated with inferior involvement.

The pathologic findings in our hearts with an electrocardiographic diagnosis of inferior infarction are similar to those reported by others.[20,25–27] Inferior myocardial infarction as defined pathologically is rarely found as an isolated lesion. A review of 12 "typical" cases with posterior myocardial infarction reported by Savage et al.[27] showed basal and medial involvement in all cases and apical involvement in 10 cases.

Anterior infarction: In cases with anteroseptal myocardial infarction, the apex was involved in all but one case. In the exceptional case, the infarct involved the anterobasal sites and related ventricular septum. The areas mainly involved in anteroseptal myocardial infarction were the middle and the apical portions of the

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anterior left ventricular wall and septum. Additional involvement of anterolateral sites seen pathologically was not revealed in the electrocardiogram. We found no electrocardiographic clues for identifying apical involvement in the presence of anteroseptal myocardial infarction. Apical involvement is common in anteroseptal myocardial infarction and its presence can be assumed in nearly every case with a diagnosis of anteroseptal myocardial infarction.

In 5 of 10 cases the diagnosis of anteroseptal myocardial infarction was based on a relatively weak Minnesota code (1-2-8). This code is characterized by a decreased R wave amplitude in the precordial leads. Our findings in anteroseptal myocardial infarction are in agreement with those reported previously.[11-13,20,21,24,25,27,29,30] The reported cases are comparable with ours and frequently have lateral, inferior or anteroseptal involvement in addition to the anteroseptal infarct, as in 10 of 12 cases reported by Savage et al.[27]

In the six cases with electrocardiographically diagnosed anterolateral myocardial infarction, the QRS complex was wide except in one case with a QRS duration of 0.10 second. Apical involvement was present in all four patients with atypical left bundle branch block and anterolateral myocardial infarction. Our findings agree with those of Horan et al.,[7] who have reported extensive apical and anteroseptal infarction in the presence of left bundle branch block with Q waves in leads I, aVL, V_5 and V_6. Except for one case, lateral involvement was part either of anterolateral or inferolateral involvement.

When the electrocardiographic diagnosis of combined anteroseptal and anterolateral myocardial infarction was made, four of seven cases had a prolonged QRS duration. Three exhibited an atypical left bundle branch block and one a right bundle branch block pattern. Apical involvement was present in each of the seven cases. Pathologically, lateral involvement was present in five cases. In two cases, there was no lateral involvement. Anterior left ventricular wall involvement in the form of anteroseptal, anterobasal and apical was present in five cases. In two cases with an electrocardiographic diagnosis of anteroseptal myocardial infarction, only the inferolateral or apical inferolateral portions of the left ventricle were involved.

Combined inferior and anterior infarction: When an electrocardiographic diagnosis of both inferior and anteroseptal myocardial infarction is made, there is usually extensive involvement of anterior and inferior walls of the left ventricular wall. Observations related to the electrocardiographic identification of isolated anteroseptal and inferior infarction also apply to their combination. In two cases, inferior myocardial infarction was diagnosed with the electrocardiogram, but pathologic studies revealed apical circumferential without inferior involvement. Furthermore, there was apical involvement in all cases with an electrocardiographic diagnosis of combined inferior and anteroseptal myocardial infarction. In contrast to previous claims,[14,20,22,27,31] we found no electrocardiographic markers to identify apical involvement. In 8 of 11 cases in this group, the diagnosis of anteroseptal infarction was based on relatively weak (1-2-8 or 1-2-7) codes.

In each of the three cases with an electrocardiographic diagnosis of inferior and anterolateral myocardial infarction, the QRS duration was prolonged. Two cases had an atypical left bundle branch block and one a right bundle branch block pattern. There was inferior involvement in the form of inferior or inferobasal infarct in all three cases. Anterolateral or lateral involvement was present in two cases, and apical circumferential involvement in the third.

Intraventricular conduction delay in the form of atypical left bundle branch block occurred frequently in cases with a diagnosis of anterolateral myocardial infarction alone or in combination with other infarcts. Such cases exhibit Q waves in leads I and aVL, and sometimes in leads V_5 and V_6.

Acute myocardial infarction: Acute myocardial infarction alone or in combination with healed infarcts was present in 10 cases. The acute myocardial infarction was transmural in two and subendocardial in the remaining eight cases (four limited, four extensive). There was S-T segment elevation corresponding to the area involved in three cases, S-T depression and T wave inversion in six cases and only flat T waves in one case. In the latter case there was a limited acute apical anterior subendocardial infarct.

Intraventricular conduction defects: Forty percent of patients (16 of 40) with apical involvement had increased QRS duration (15 had "atypical" or "typical" left bundle branch block, whereas 1 had right bundle branch block). Thirty percent of patients (3 of 10) with no apical involvement had increased QRS duration (1 patient had intraventricular conduction delay, and 2 had right bundle branch block). Thus, 38 percent of patients (19 of 50) in this study had increased QRS duration. The incidence of increased QRS duration was 6 percent (1 of 16) in single infarcts, 44 percent (8 of 18) in patients with two areas involved, 37 percent (7 of 19) in patients with three areas involved and 43 percent (3 of 7) in patients with four areas involved. Thus, there were three subjects with right bundle branch block, nine with left bundle branch block and seven with intraventricular conduction delay. The septum and parts of the septum closely related to the conduction system were involved in every case except one with intraventricular conduction delay and apical lateral infarction. These observations support previous findings of septal and apical infarction when the electrocardiogram shows a left bundle branch block pattern with abnormal Q waves.[26] Although both electrocardiographic and vectorcardiographic criteria for the diagnosis of myocardial infarction in the presence of left bundle branch block have been described, these should be used with caution because of many false positive results.[7,26,32-39]

Q waves in subendocardial infarction: Our findings regarding the incidence of abnormal Q waves in subendocardial infarction agree with previous data.[11,12,14,25-27] The majority of our cases had subendocardial myocardial infarction. Although it has been

repeatedly shown that subendocardial infarcts, even very small ones, can produce abnormal Q waves,[40] the electrocardiographers have traditionally ascribed abnormal Q waves to transmural myocardial infarction.

Implications: The electrocardiographic localization of myocardial infarction based on Minnesota codes (inferior, anteroseptal, anterolateral) appears more reasonable than the numerous localizations suggested in previous reports (septal, anteroseptal, anterior, lateral, high lateral, inferior, true posterior, apical, and so forth). The 12 lead electrocardiogram does not provide adequate information for such detailed and exact classification.

Our study indicates that, in general, the electrocardiographic recognition of myocardial infarction (Minnesota codes 1-1, 1-2, 1-3) is reasonably good. The recognition of general localization is fair. However, as previously reported,[18,25–27] the recognition of the exact extent of myocardial involvement is poor. There is frequently extension of the infarct into areas adjacent to the main infarct. Such extensions usually are not recognized in the electrocardiogram. Although the sensitivity (percent of cases with myocardial infarction diagnosed as myocardial infarction) of electrocardiographic criteria used in this study appears to be good, the specificity (percent of noninfarct cases diagnosed as nonmyocardial infarction) is not known.

It has been suggested that in the presence of anterior myocardial infarction, a normal R wave in leads V_4 to V_6 represents anterior apical, a markedly diminished R wave implies intermediate apical and an abnormal Q wave represents apical circumferential involvement. Our studies do not justify such a conclusion. In the presence of anteroseptal myocardial infarction or combined anteroseptal and anterolateral myocardial infarction, one can assume with high probability that there is apical involvement.

Whether other methods of recording the electrical potentials of the heart, such as vectorcardiography or body surface mapping, will provide information regarding the location and extent of myocardial infarction superior to that provided by the 12 lead electrocardiogram is not known. There are limitations to the use of various electrocardiographic terms related to the location and extent of myocardial infarcts. These need to be recognized.

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Apex Sector Echocardiography in Evaluation of the Right Atrium In Patients With Mitral Stenosis and Atrial Septal Defect

FREDERICK G. KUSHNER, MD*
WILFRED LAM, MD*
JOEL MORGANROTH, MD, FACC

Philadelphia, Pennsylvania

Cross-sectional echocardiography utilizing the four chamber apical view was used to evaluate right atrial dimensions as a means of detecting abnormal right heart hemodynamics in 20 patients with mitral stenosis, 5 patients with an atrial septal defect and 10 patients without heart disease. Right and left atrial dimensions on apex echocardiography were 40 mm or less in control subjects. There was a good correlation ($r = 0.81$) between left atrial size assessed with apex sector and M mode echocardiography. In patients with an atrial septal defect, the left atrium was of normal size on apex sector echocardiography; in patients with mitral stenosis, it was larger on apex echocardiography (59 ± 9 mm) than on M mode echocardiography (51 ± 8 mm).

The right atrium was enlarged (54 ± 5 mm) on apex echocardiography in all five patients with an atrial septal defect, but the right ventricle was enlarged in only four. Seventeen of 20 patients with mitral stenosis had an enlarged right atrium (53 ± 7 mm) on apex echocardiography, whereas 15 had normal right ventricular dimensions (21 ± 9 mm) on M mode echocardiography. Right atrial size on apex echocardiography was enlarged (54 ± 6 mm) in 10 of 11 patients with mitral stenosis and pulmonary arterial hypertension. Thus, evaluation of the right atrial dimension with apex echocardiography may be more sensitive than M mode echocardiography in detecting early right heart involvement in specific cardiac conditions.

Although the right atrium can be identified with M mode echocardiography, a reliable assessment of its dimensions has not been possible with this technique.[1] Cross-sectional echocardiographic methods have identified both the atria and ventricles as well as the ventricular and interatrial septa.[1–5] Utilizing a cross-sectional view derived by placing the transducer on the cardiac apex, one can simultaneously visualize the right and left atria, right and left ventricles and interatrial and interventricular septa and accurately measure the right and left atria.[2] This view has been termed the four chamber apical view or the hemiaxial equivalent view. We will refer to it as apex sector echocardiography. The apex sector echocardiogram represents a cross-sectional plane recorded just posterior to the aorta and the aortic valve (Fig. 1).

This report describes our investigation into the potential usefulness of measuring right and left atrial dimensions with apex sector echocardiography to detect abnormal right heart hemodynamics.

Material and Methods

Patients: Thirty-five patients were evaluated with a history, physical examination, standard 12 lead electrocardiogram, chest X-ray film and both a standard M mode and an apex sector echocardiogram (Table I). There were three groups of patients. Group 1 consisted of 10 control subjects, including 7 men,

From the Echocardiography Laboratory, Hospital of the University of Pennsylvania and the Cardiovascular Section, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

*Drs. Kushner and Lam were Research Fellows of the American Heart Association Southeastern Pennsylvania Affiliate when this study was prepared. Manuscript received April 18, 1978; revised manuscript received June 6, 1978, accepted June 7, 1978.

Address for reprints: Joel Morganroth, MD, 2202 Research Building, Lankenau Hospital, City Line and Lancaster Avenues, Philadephia, Pennsylvania 19151.

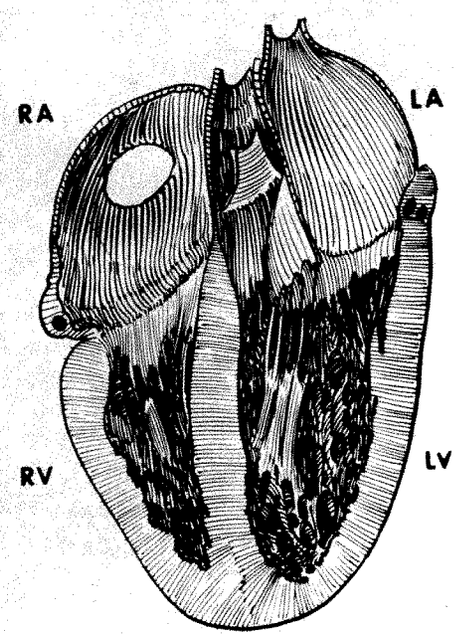


FIGURE 1. The apex sector echocardiogram represents a cross-sectional plane just posterior to the aorta and aortic valve as shown in this schematic anatomic section. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

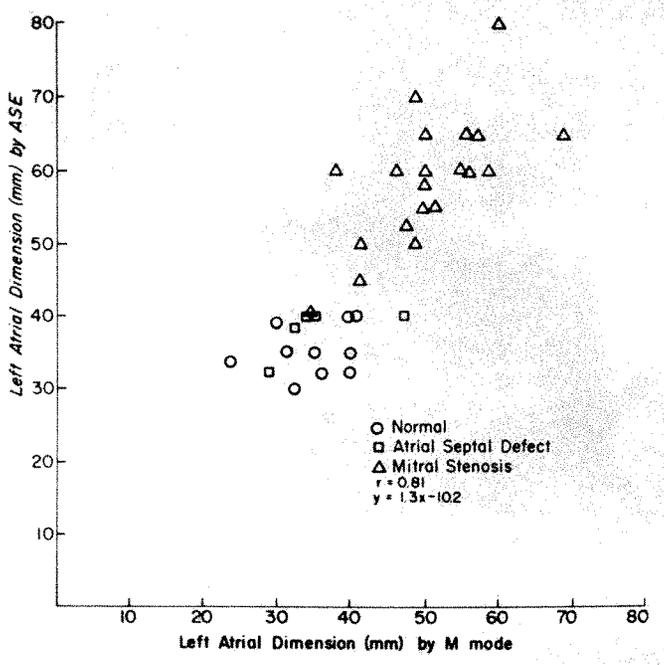


FIGURE 2. Left atrial dimension determined with M mode echocardiography plotted against left atrial dimension determined with apex sector echocardiography (ASE) in control subjects **(circles)**, subjects with an atrial septal defect **(squares)** and subjects with mitral stenosis **(triangles)**.

who had no evidence of cardiac disease. Six of these 10 patients had been referred for cardiac catheterization and coronary angiography for evaluation of chest pain and had had normal studies. The remaining four patients were young subjects clinically free of any cardiovascular symptoms or abnormal noninvasive tests. None had mitral valve prolapse. Group 2 consisted of five patients (three male) with an atrial septal defect and a left to right intracardiac shunt greater than 1.5:1.0 determined with cardiac catheterization in each case. Group 3 consisted of 20 patients with mitral stenosis, including 18 women, 11 of whom underwent cardiac catheterization.

Echocardiography: *M mode echocardiography* was performed in the standard manner with a commercially available Ekoline 20 A (Smith Kline Instruments) interfaced with a Honeywell 1858 Visicorder. Right and left ventricular internal dimensions were measured at end-diastole at the peak of the R wave. The internal left atrial dimension was recorded at end-systole at the level of the aortic valve.

The cross-sectional echocardiographic instrument used in this study was a commercially available mechanical 30° sector scanner (Smith Kline Instruments Eko-Sector I). Cross-sectional echocardiographic studies were performed in the supine or left lateral position with the transducer placed in the third or fourth intercostal space to the left of the sternum. The apical view was recorded by positioning the transducer on the left ventricular apex, which was identified with palpation. The probe was directed toward the base of the heart parallel to the long axis of the left ventricle and perpendicular to the plane of the interventricular septum. The probe was angled in a cephalad-caudad direction until maximal atrial dimensions were recorded while all four chambers of the heart, atrial and ventricular septa and the cardiac apex were simultaneously visualized in the sector recording.

Satisfactory apex sector echocardiograms were obtained in 80 percent of patients. Inadequate studies were observed in subjects who had a massively enlarged heart with an apex to base dimension greater than the depth of field of the sector (15 cm) and in subjects with chest deformities or chronic obstructive pulmonary disease. The ability to palpate the apex of the heart aided in successfully obtaining the apical view.

Using the Eko Sector I, the apex of the heart is displayed at the top of the sector recording. The right and left atria form the base of the sector with their respective ventricles and atrioventricular (A-V) valve rings above. The right atrium and ventricle are on the left of the recording. The dimensions of the atria were measured from the A-V valve rings (tricuspid or mitral valve insertions) to the posterosuperior atrial roofs at end-systole by consensus of two observers who had no prior knowledge of diagnosis or laboratory data. An internal cursor with centimeter markings was positioned directly on the cross-sectional echocardiogram for accurate dimensional analysis.

M mode and cross-sectional data were obtained within 12 hours of each other in each patient, and cardiac catheterization data were obtained in 22 of the 35 patients within 2 weeks of the echocardiographic studies. The normal M mode left atrial and right ventricular dimensions are less than 40 mm and less than 27 mm, respectively.[1]

Results

To determine the relation between atrial size as assessed with apex sector and M mode echocardiography in normal subjects and in subjects with right ventricular pressure and volume overload states, left atrial dimensions determined with the two techniques were compared in normal subjects, subjects with atrial septal defect and subjects with mitral stenosis and pulmonary hypertension. The left atrial dimension was chosen because there is as yet no way to measure right atrial dimension with M mode echocardiography. None of the 10 control subjects had a right or left atrial dimension greater than 40 mm on apex sector echocardiography, and none had left atrial or right ventricular enlargement

TABLE I

Echocardiographic and Cardiac Catheterization Data

Case no.	Age (yr) & Sex	ASE RA (mm)	ASE LA (mm)	M Mode LA (mm)	M Mode RV (mm)	M Mode LV (mm)	Pressures (mm Hg) RA	PA	PA	PCW	Shunt
					Control Subjects						
1	43M	35	40	40	22	50	5	28/8	12	6	—
2	46M	40	32	40	14	47	5	20/8	11	8	—
3	41M	35	35	35	16	43	5	17/4	11	4	—
4	70M	30	35	31	18	44	—	—	—	—	—
5	51F	35	33	23	26	41	5	23/12	15	12	—
6	19M	32	30	32	20	49	—	—	—	—	—
7	26F	30	32	36	14	48	—	—	—	—	—
8	40M	39	39	30	22	50	5	16/8	11	6	—
9	46M	40	40	40	23	50	—	—	—	—	—
10	31F	35	35	40	19	44	3	18/5	9	4	—
Mean		35	35	35	19	47	5	0	12	7	—
± SD		± 4	± 4	± 6	± 4	± 3	± 1		± 2	± 3	
					Patients With an Atrial Septal Defect						
11	42M	60	40	47	48	42	5	28/8	14	5	2/1
12	18F	60	38	32	45	35	5	24/10	15	6	1.6/1
13	18M	52	32	29	25	40	5	23/7	14	7	3.5/1
14	35M	50	40	35	40	30	6	34/11	20	8	4.6/1
15	54F	50	40	34	30	39	5	36/12	22	5	3/1
Mean		54	38	35	38	37	5	—	17	6	2.8/1
± SD		± 5	± 3	± 7	± 10	± 5	± 1		± 4	± 1	
					Patients With Mitral Stenosis						
16	59M	60	65	57	32	42	6	40/20	30	20	—
17	64F	50	65	50	19	39	4	34/18	26	18	—
18	49F	45	55	51	17	42	—	—	—	—	—
19	54F	52	58	50	29	41	—	—	—	—	—
20	40F	50	60	50	—	—	2	46/24	30	12	—
21	67F	70	65	57	45	45	—	—	—	—	—
22	44F	50	60	59	18	50	6	84/42	55	30	—
23	49F	45	50	49	27	53	7	66/25	42	23	—
24	18M	60	80	60	21	61	10	70/40	55	20	—
25	62F	60	70	49	20	—	23	50/25	35	29	—
26	60F	60	65	69	26	43	12	130/48	70	35	—
27	35F	52	60	38	19	52	—	—	—	—	—
28	63F	45	60	46	17	41	—	—	—	—	—
29	45F	43	52	48	23	53	—	—	—	—	—
30	24F	35	40	34	13	42	—	—	—	—	—
31	36F	40	50	41	12	45	2	48/20	32	20	—
32	59F	60	60	56	18	42	5	55/26	37	29	—
33	60F	50	60	55	15	45	—	—	—	—	—
34	73F	50	55	50	12	46	—	55/30	45	30	—
35	45F	35	45	41	18	35	—	—	—	—	—
Mean		51	59	51	21	45	8	—	42	24	—
± SD		± 9	± 9	± 8	± 9	± 6	± 6		± 14	± 7	

ASE = data derived from apex sector echocardiography; LA = left atrium; LV = left ventricle; M Mode = M-mode echocardiography; PA = pulmonar arterial; PA = mean pulmonary arterial; PCW = pulmonary capillary wedge; RA = right atrium; RV = right ventricle; Shunt = magnitude of le to right shunt at the atrial level.

on M mode echocardiography (Table I). Six of the normal subjects who underwent cardiac catheterization were found to have normal left and right heart hemodynamics and to be free of any coronary artery disease.

Left atrial size: Figure 2 shows the left atrial size determined with apex sector and M mode echocardiography in all groups. The correlation coefficient between the left atrial sizes determined with the two techniques was 0.81, which was statistically significant ($P < 0.01$). The mean left atrial size on apex sector echocardiography was 35 ± 6 mm in control subjects and normal (mean 38 ± 3 mm) in all patients with an atrial septal defect. Eighteen of 20 patients with predominant mitral stenosis had an enlarged left atrium (mean 51 ± 8 mm) on M mode echocardiography. Among the two patients with a normal left atrial size on M mode echocardiography, apex sector echocardiography demonstrated an enlarged left atrium (60 mm) in one and a left atrial size of 40 mm in the other. Left atrial dimension was larger on apex sector echocardiography than on M mode echocardiography in all patients with mitral stenosis.

Right atrial size: To determine the relation between right heart hemodynamics and right atrial size, mean pulmonary arterial pressure for all subjects with cardiac catheterization data was compared with right atrial size on apex sector echocardiography (Fig. 3). All control subjects had both normal right atrial dimensions (mean 35 ± 4 mm) on apex sector echocardiography and normal mean pulmonary arterial pressures (mean 12 ± 2 mm Hg). All five patients with an atrial septal defect had an enlarged right atrium (mean 54 ± 5 mm) on apex sector echocardiography. In three of these five patients mean pulmonary arterial pressure was normal and in two it was minimally elevated. All 11 patients with mi-

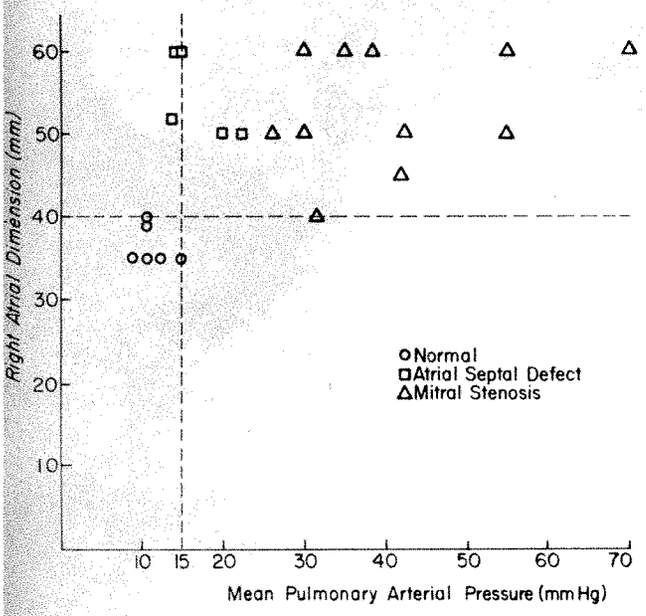


FIGURE 3. Mean pulmonary arterial pressure versus the right atrial dimension assessed with apex sector echocardiography is plotted for control subjects **(circles)**, subjects with an atrial septal defect **(squares)** and subjects with mitral stenosis **(triangles)**.

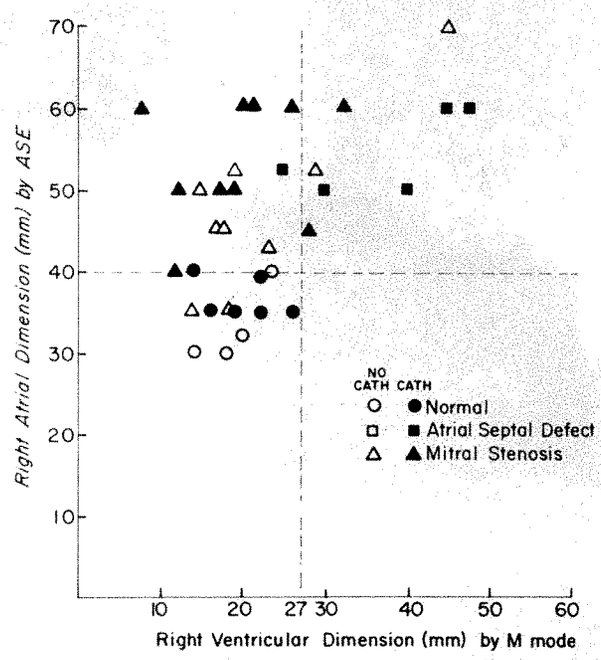


FIGURE 4. Right ventricular internal dimension determined with M mode echocardiography plotted against right atrial dimension assessed with apex sector echocardiography (ASE) for control subjects **(circles)**, subjects with an atrial septal defect **(squares)** and subjects with mitral stenosis **(triangles)**. **Solid figures** represent those subjects who had undergone cardiac catheterization (CATH).

tral stenosis who had undergone cardiac catheterization had an elevated mean pulmonary arterial pressure (mean 42 ± 14 mm Hg), and 10 of the 11 had an enlarged right atrium on apex sector echocardiography (54 ± 6 mm).

Right atrial versus right ventricular size: To assess whether the right atrial dimension on apex sector echocardiography was more sensitive than the right ventricular dimension measured with M mode echocardiography in detecting abnormal right heart hemodynamics, these two chamber measurements were compared in all three groups of subjects (Fig. 4). All control subjects demonstrated normal right atrial dimensions on apex sector echocardiography and concomitant normal right ventricular internal dimensions (mean 19 ± 4 mm) on M mode echocardiography. All five patients with an atrial septal defect had a large left to right shunt (greater than 1.5:1), and in four patients the right ventricular internal dimension on M mode echocardiography was enlarged (mean 41 ± 8 mm). The right atrium on apex sector echocardiography was enlarged in all patients with an atrial septal defect (mean 54 ± 5 mm). In patients with mitral stenosis the right ventricular internal dimension could be accurately measured in 19 of 20 patients. In 15 of these 19 patients (79 percent), the right ventricular internal dimension was normal (mean 21 ± 9 mm) on M mode echocardiography. However, the right atrial dimension on apex sector echocardiography was increased in 17 patients (mean 53 ± 7 mm). Ten of the 11 patients with mitral stenosis who had undergone cardiac catheterization had a measurable right ventricular internal dimension on M mode echocardiography. Although 9 of these 10 patients had a normal right ventricular internal dimension on M mode echocardiography, 8 had an enlarged right atrium on apex sector echocardiography (mean 54 ± 6 mm). The patient with an enlarged right ventricle had an enlarged right atrium. The patient with a normal right atrium on apex sector echocardiography had a normal right ventricular size on M mode echocardiography. In all patients with an abnormal right atrium on apex sector echocardiography, the left atrium was also abnormal. Figure 5 shows representative apex sector echocardiograms obtained in the two patient groups and the control subjects.

Discussion

With the advent of cross-sectional echocardiography, visualization of the right atrium and the interatrial septum, previously not possible with M mode echocardiography, became possible. However, right atrial dimensional analysis has not been specifically calculated using routine long axis or short axis views of cross-sectional echocardiography.[3–6]

Right atrial size and right heart hemodynamics: The use of apex sector echocardiography to evaluate patients with right ventricular volume overload (atrial septal defect) and right ventricular pressure overload (pulmonary hypertension due to mitral stenosis) has demonstrated that the right atrial measurement may be an early marker of abnormal right heart hemodynamics. In right ventricular volume overload states, the right ventricular internal dimension on M mode echocardiography and the right atrial dimension on apex sector echocardiography were usually both enlarged despite normal pulmonary arterial pressures. In contrast, in right ventricular pressure overload, the right ventricular dimension on M mode echocardiography

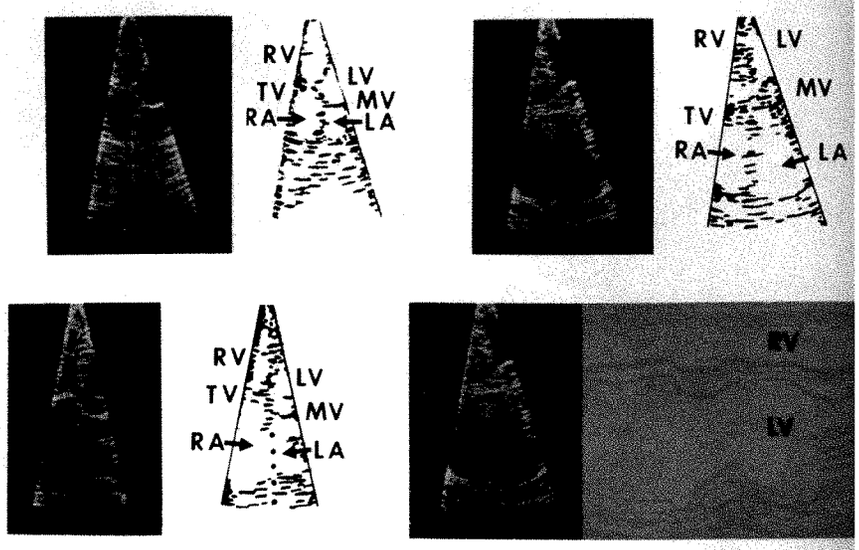


FIGURE 5. Four representative apex sector echocardiograms positioned specifically to show the right atrium (RA) in detail. The **upper left panel** is from a control subject, the **upper right panel** from a subject with mitral stenosis and the **lower left panel** from a subject with an atrial septal defect. In the **lower right panel** an apex sector echocardiogram from a subject with mitral stenosis demonstrating an enlarged right atrium is compared with the subject's corresponding M mode echocardiogram, which indicated a normal-sized right ventricle (RV). LA = left atrium; LV = left ventricle; MV = mitral valve anulus; TV = tricuspid valve anulus.

was usually normal, whereas right atrial size in apex sector echocardiography was generally enlarged. These findings may be analogous to the left atrial and left ventricular dimensional changes in left ventricular volume and pressure overload states. For example, in patients with systemic hypertension, the left ventricular internal dimension may not be increased in the presence of left atrial dilatation. Thus, the detection of an enlarged right atrium on apex sector echocardiography may be an earlier echocardiographic marker than right ventricular dimension on M mode echocardiography in detecting right heart abnormalities, particularly in conditions associated with right ventricular pressure overload.

Possible limitations of study: Unfortunately, a specific reference standard for right atrial size does not exist. Weinnert et al.,[7] using a 90° phased array cross-sectional echocardiogram, described the potential of using an apical view of the cross-sectional echocardiogram to measure right atrial dimension. Right atrial measurements were validated using plaster casts of actual specimens. We could not validate our measurements of right atrial dimension with angiography because right atrial angiograms were not available, and it is not clear that volume calculations with angiography, which uses formulas derived for a prolate ellipsoid, would be an accurate measure of a nongeometrically shaped right atrial chamber. We compared measurements of left atrial size made with apex sector and M mode echocardiography to obtain a parallel standard between these two echocardiographic techniques. A good correlation ($r = 0.81$) was found between the two measurements, although left atrial size was slightly larger with the apex sector than with the M mode echocardiographic method. Previous determinations of left atrial size using M mode echocardiography[8] and biplane angiography[9] demonstrated asymmetry in the geometry of the left atrium particularly when the chamber dilated in disease states; this observation may account for our finding.

We used a commercially available 30° mechanical scanner and thus could measure right atrial size in only one dimension because the full extent of lateral right atrial dimension could not be visualized. It is possible that changes in other atrial axes may occur earlier during atrial enlargement than in the axis measured in our study.

Acknowledgment

We express appreciation to Patricia Klunder for technical assistance, John A. Kastor, MD for manuscript review and Eileen Golden for secretarial assistance.

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Effect of Catheter Position on the Initiation of Atrial Echoes With Atrial Pacing and Premature Stimulation in Patients With Accessory Pathways

EDWARD L. C. PRITCHETT, MD
DAVID G. BENDITT, MD
WILLIAM M. SMITH, PhD
JOHN J. GALLAGHER, MD

Durham, North Carolina

Eleven patients with an accessory pathway and reciprocating tachycardia were studied using both fixed rate atrial pacing and the atrial extrastimulus technique. Six of the patients had an accessory pathway that conducted in both the anterograde and retrograde direction; but the effective refractory period of their accessory pathway in the anterograde direction was relatively long and was greater than the longest coupling intervals that initiated atrial echoes. Five patients had an accessory pathway that conducted only in the retrograde direction.

The extrastimulus technique could be used with stimulation sites near to and remote from the accessory pathway in 10 of the 11 patients. Atrial echoes were initiated by a single atrial extrastimulus at both sites in 7 of the 10 patients, and in each patient the upper limit of the echo zone was longer with stimulation at the site near the accessory pathway. In the other three patients atrial echoes were initiated only during stimulation at the site near the acessory pathway because either atrial refractoriness or atrioventricular nodal refractoriness was encountered before the echo zone was entered during stimulation at the site remote from the accessory pathway.

Differences in the longest cycle length that initiated an atrial echo during fixed rate atrial pacing were similarly demonstrated in three patients. In these three patients, pacing at the site near the accessory pathway initiated echoes at a longer cycle length than pacing at the site remote from the accessory pathway. In three other patients the electrophysiologic characteristics of atrioventricular conduction prevented a demonstration of these differences. Catheter position is an important variable in the initiation of atrial echoes in patients with accessory pathways.

From the Division of Cardiology, Duke University Medical Center, Durham, North Carolina. This study was supported in part by Grant RR-30 from the General Clinical Research Center Branch, Division of Research Resources and by Grant HL 151901 from the National Institutes of Health, Bethesda, Maryland. This work was done in part during the tenure of Dr. Benditt as a Fellow of the Medical Research Council of Canada. Dr. Pritchett is the recipient of Young Investigator Research Award 1R23 HL21347-01 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. This work was done during Dr. Gallagher's tenure as an Established Investigator for the American Heart Association, Dallas, Texas. Manuscript received April 18, 1978; revised manuscript received June 13, 1978, accepted June 14, 1978.

Address for reprints: Edward L. C. Pritchett, MD, PO Box 3477, Duke University Medical Center, Durham, North Carolina 27710.

In patients with the Wolff-Parkinson-White syndrome the common reentrant tachycardia results from conduction in the anterograde direction over the atrioventricular (A-V) node and conduction in the retrograde direction over an accessory pathway. During sinus rhythm A-V conduction in the anterograde direction over the accessory pathway causes preexcitation of a portion of the ventricle and the typical configuration of the QRS complex (with a delta wave). The easily recognized difference between the configuration of the preexcited complexes recorded during sinus rhythm and the normal QRS configuration recorded during reentrant tachycardia makes the Wolff-Parkinson-White syndrome an ideal model in which to study reentrant arrhythmias. In the usual conceptual model of a reentrant arrhythmia, unidirectional block and slow conduction are postulated to occur in distinct limbs of the circuit.[1] In patients with the Wolff-Parkinson-White syndrome, if premature atrial stimuli are introduced at progressively shorter coupling intervals, the onset of block in the accessory pathway is easily identified

by the appearance of a normal QRS configuration; and catheter recordings demonstrate slow conduction over the A-V node in these early complexes.[2]

In the original description of premature atrial stimulation in the Wolff-Parkinson-White syndrome, premature stimuli at all coupling intervals that were conducted to the ventricles exclusively over the A-V node initiated atrial echoes.[3] However, in another group of patients with accessory pathways, premature atrial stimuli at some coupling intervals were conducted exclusively over the A-V node but failed to initiate echoes.[4,5] In these patients, progressive shortening of the coupling interval eventually resulted in the initiation of echoes. Three such patients were reported on in a description of the types of echo zones in 45 patients studied with the extrastimulus technique.[4] In those three patients the longest coupling interval initiating an atrial echo was shifted to a longer coupling interval by stimulating at the site close to the accessory pathway. In this report we describe the results obtained in 11 such patients studied with both the atrial extrastimulus and fixed rate atrial pacing techniques. The data confirm the importance of catheter position as a variable in the initiation of atrial echoes.

Methods

All 11 patients had been referred to the Duke University Medical Center for treatment of recurrent arrhythmias and were studied in The Clinical Electrophysiology Laboratory with techniques described previously.[6,7] Each patient was shown to have a reentrant tachycardia that used the atrioventricular (A-V) node for conduction in the anterograde direction and an accessory pathway for conduction in the retrograde direction.[8–10] The location of the accessory pathway was determined in each patient at the beginning of the procedure with use of endocardial mapping.[6,10]

Electrophysiologic procedures: As part of each study, refractory periods were measured using the extrastimulus technique (stimulator designed and constructed by Mr. Jackie Kasell) with catheters positioned in both the right atrium and the coronary sinus. In making these measurements every eighth paced complex was followed by an induced premature stimulus at progressively shorter coupling intervals until atrial refractoriness was reached. When the coupling interval of the extrastimulus approached a critical value (anterograde effective refractory period of the accessory pathway, upper limit of the echo zone, effective refractory period of the atrium, and so forth), 10 msec decrements were used and coupling intervals were repeated. Data were simultaneously recorded on magnetic tape at 3 3/4 inches/sec (9.525 cm/sec) and written at 200 mm/sec using a Mingograph-800 eight channel ink-jet recorder. The written records were measured using an interactive computer program,[11] with which blinded observers can make measurements that are reproducible within 2 msec.

The effect of the pacing site on the cycle length that initiated echoes during fixed rate atrial pacing also was assessed. The pacing cycle length was gradually decreased from the longest cycle length at which sinus competition did not occur until atrial echoes were first initiated, Wenckebach conduction in the A-V node was observed or a cycle length of 240 msec was reached. When the longest cycle length that initiated echoes was approached, 10 msec or 20 msec decrements were used.

Definitions and symbols: S_1, A_1, H_1 and V_1 refer to the stimulus, atrial electrogram, His bundle electrogram and ventricular electrogram of the basic drive beat. S_2, A_2, H_2 and V_2 refer to the same deflections of the induced extra beat. CSA and CSV refer to the atrial and ventricular electrograms recorded from a catheter in the coronary sinus. HBEA and HBEV refer to the atrial and ventricular electrograms recorded from the catheter positioned over the bundle of His.[12] RA refers to the electrogram recorded from a catheter in the right atrium, and RV to the electrogram recorded from a catheter in the right ventricular apex. A_{E1} refers to the atrial electrogram of the first atrial echo after an induced premature beat.

Anterograde effective refractory period of the accessory pathway: The longest A_1-A_2 interval not conducted with ventricular preexcitation. This measurement is made from a catheter positioned near the accessory pathway.[2]

Functional refractory period of the atrium: The shortest A_1-A_2 interval attainable at a specified site.[13]

Effective refractory period of the A-V node: The longest A_1-A_2 interval not followed by an H_2.[14] If the longest A_1-A_2 interval not followed by an H_2 is also the anterograde effective refractory period of the accessory pathway, the effective refractory period of the A-V node is equal to or greater than the measured interval.

Anterograde echo zone: All coupling intervals (A_1-A_2) with which A_2 is conducted to the ventricles without preexcitation, returns to the atrium using the accessory pathway and initiates an atrial echo (A_{E1}).

Upper limit of the echo zone: The *longest* coupling interval (A_1-A_2) with which A_2 is conducted to the ventricle without preexcitation, returns to the atrium using the accessory pathway and initiates an atrial echo (A_{E1}).[4] With coupling intervals that do not cause intraatrial conduction delays, this measurement can be made using any catheter in the atrium. Atrial electrograms are routinely recorded from three sites (lateral right atrium, low septal right atrium and coronary sinus), and this measurement is most conveniently measured using recordings from the catheter closest to the accessory pathway.

Echo time: A_2-A_{E1} is the interval between the atrial electrograms of the induced premature beat (A_2) and the first atrial echo (A_{E1}) recorded at a specified site during stimulation at a specified site. The *minimal echo time* is the shortest attainable A_2-A_{E1} recorded by a catheter positioned near the accessory pathway.[4]

Enhanced A-V nodal conduction[15]*:* A type of A-V nodal conduction in which (1) the A-H interval in sinus rhythm is less than or equal to 60 msec; (2) 1:1 A-V nodal conduction is maintained during atrial pacing at a cycle length of less than 300 msec; and (3) the difference between the A-H interval measured during sinus rhythm and the A-H interval measured during atrial pacing at a cycle length of 300 msec is less than or equal to 100 msec.

Dual A-V nodal pathways[16]*:* A type of A-V nodal conduction described by a discontinuity in the curve relating H_1-H_2 intervals to their associated coupling interval (A_1-A_2).

Patient selection: The 11 patients presented met the following criteria:

1. Reciprocating tachycardia induced during the study used the A-V node for conduction in the anterograde direction and an accessory pathway for conduction in the retrograde direction.[8–10]

2. The accessory pathway was located in the parietal A-V groove (that is, not in the septum).[17] If an accessory pathway is located in the septum, the distinction between near and remote pacing sites is difficult.

3. The upper limit of the echo zone was not accompanied by bundle branch block in the ventricle containing the accessory pathway. (This phenomenon has been shown to shift

TABLE I

Refractory Periods and Echo Zone Limits (in msec) in 10 Patients

Case no.	Accessory Pathway	Pacing Site	Cycle Length	FRP* Atrium	Minimal Echo Time	ERP Accessory Pathway	Upper Limit Echo Zone	ERP A-V Node	FRP A-V Node
1	Left	CS	600	264	271	>600	315	<264	≤361
		RA	600	. . .	261	>600	298	<260	≤334
		CS	400	260	268	>400	279	<260	≤325
2	Left	CS	600	255	265	>600	355	310/260†	360/490†
		RA	600	. . .	250	>600	315	360/490†	360/510†
3	Right	CS	800	. . .	288	424	374	337/313†	423/592†
		RA	800	302	311	429	399	391/345†	471/607†
4	Left	CS	400	190	205	None	270	210	270
		RA	400	. . .	230	None	245	<225	≤300
5	Left	CS	700	260	270	None	325	<265	≤315
		RA	700	. . .	No echo	None	No echo	<320	<365
6	Left	CS	400	199	211	None	248	213	268
		RA	400	. . .	No echo	None	No echo	219	261
7	Left	CS	600	275	‡	330	330	§	§
		RA	600	. . .	295	330	290	<285	≤370
8	Right	CS	600	. . .	No echo	None	No echo	370	435
		RA	600	295	430	None	400	370	435
9	Left	CS	800	260	310	618	460	<260	≤370
		RA	800	. . .	300	592	375	<265	≤405
10	Right	CS	700	302	394	‖	397	<302	≤410
		RA	700	281	295	‖	527	302	402

* Measured for site near the accessory pathway.
† Fast pathway/slow pathway.
‡ Upper limit of echo zone equaled the effective refractory period of the accessory pathway.
§ Could not be measured because of ventricular preexcitation.
‖ 2:1 block in accessory pathway during pacing prevented measurement.
A-V = atrioventricular; CS = coronary sinus; ERP = effective refractory period; FRP = functional refractory period; RA = right atrium.

the upper limit of the echo zone to longer coupling intervals.[4])

4. Either (a) no ventricular preexcitation was present during sinus rhythm, and none was induced by pacing in the right atrium or coronary sinus; or (b) ventricular preexcitation was present but the effective refractory period of the accessory pathway in the anterograde direction exceeded the upper limit of the echo zone when measured using at least one of the two stimulation sites. We have previously described this as a type III echo zone.[4] Wellens[5] has used a different classification and described this same phenomenon as type 3.

Results

Effect of catheter position on the initiation of atrial echoes with the extrastimulus technique: Table I summarizes the results obtained with the extrastimulus technique in the 10 patients in whom the technique could be used at both atrial sites. Patients 4, 5, 6 and 8 had no ventricular preexcitation and met criterion 4a. The remaining patients had ventricular preexcitation and met criterion 4b. The results in these two groups were similar and are presented together.

Changing the stimulation site changed the upper limit of the echo zone in all 10 patients. In seven patients the upper limit of the echo zone could be measured exactly using both stimulation sites and at least one cycle length. In these seven patients the upper limit of the echo zone was shifted to longer coupling intervals by stimulation at the site near the accessory pathway. The average magnitude of this shift was 51 msec, and the longest shift observed was 130 msec. The data from these seven patients are depicted in Figure 1 as lines with filled circles in the right column. Several different cycle lengths of stimulation are represented. In one of these seven patients the upper limit of the echo zone was the effective refractory period of the accessory pathway using stimulation at the site near to the accessory pathway (Fig. 1).

In 3 of the 10 patients no echo zone was described using stimulation at the site remote from the accessory pathway because either the effective refractory period of the A-V node or the functional refractory period of the atrium was encountered before the echo zone was entered. In Figure 1, the lines representing data from these patients depict only the minimal shift possible.

Effect of stimulation site on the initiation of atrial echoes by fixed rate atrial pacing: The effect of pacing site on the initiation of atrial echoes by pacing at progressively shorter cycle lengths was systematically studied in six patients. In three of these patients a distinct difference was demonstrated in the longest cycle length that induced an atrial echo. Patient 10 had an accessory pathway located in the right anterior paraseptal region. Atrial echoes were first induced during pacing of the right atrium at a cycle length 40 msec

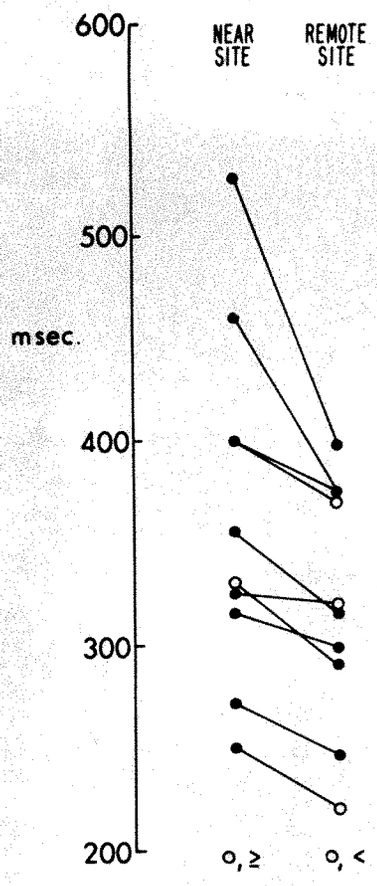


FIGURE 1. Upper limit of the echo zone measured at near and remote pacing sites in 10 patients. The single **open circle** in the **left column,** representing measurements made at the near site, indicates that in Patient 7 the upper limit of the echo zone at the near site was the effective refractory period of the accessory pathway. The three **open circles** in the **right column,** representing measurements made at the remote site, indicate that atrial or atrioventricular nodal refractoriness was encountered before the echo zone was entered.

longer than the cycle length required to initiate echoes during coronary sinus pacing. Figures 2 to 4 show the effect of right atrial and coronary sinus pacing on the A-H interval and the initiation of tachycardia in this patient. With right atrial pacing, atrial echoes were initiated when the cycle length was shortened from 420 to 400 msec (Fig. 3). With coronary sinus pacing, atrial echoes were first observed when the pacing cycle length was shortened from 380 to 360 msec (Fig. 4). Patient 4 had an accessory pathway located in the left A-V groove and reciprocating tachycardia was initiated during coronary sinus pacing at a cycle length of 330 msec and during right atrial pacing at a cycle length of 280 msec.

Patient 11 was unique and is not included in Table I. In this patient an accessory pathway was located in the left A-V groove and conducted only in the retrograde direction. Consistent pacing was not possible at the near site because any stimulus applied in the coronary sinus induced an atrial echo. Figure 5 shows sinus rhythm with a cycle length of 655 msec. The A-H interval during the sinus rhythm was 75 msec. A single stimulus was applied in the coronary sinus during late diastole so that the RA-RA coupling interval was 620 msec. The A-H interval of the induced beat was 65 msec and an atrial echo was initiated. Using pacing in the right atrium, no echoes were induced until the pacing cycle length was shortened to 360 msec (Fig. 6).

The electrophysiologic characteristics of A-V conduction prevented demonstration of any shifts during straight pacing in the three other patients. Patient 1 manifested enhanced conduction in the A-V node, and no echoes were induced by pacing at either site. In Patients 2 and 7, echoes were initiated by, respectively, the onset of sudden prolongation of the A-H interval and block in the accessory pathway. These two events occurred at similar cycle lengths in the respective patient

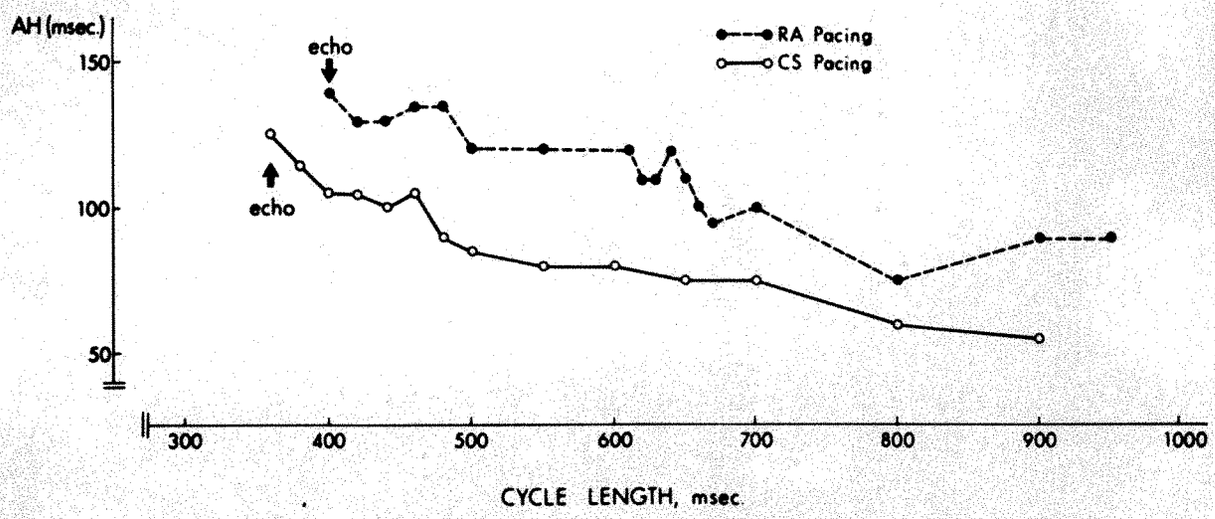


FIGURE 2. Patient 10. The response of the A-H interval to fixed rate atrial pacing using the right atrium (RA) and coronary sinus (CS). The two curves are approximately parallel,[20] but atrial echoes first were initiated at a cycle length 40 msec longer during right atrial pacing. In this patient an accessory pathway was located in the right parietal atrioventricular groove.

and therefore echoes were first initiated in these two patients at similar cycle lengths.

Relation of the functional refractory period of the atrium to the minimal echo time: In Patients 1 to 7 there was a close relation between the functional refractory period of the atrium measured using stimulation at the near site and the minimal echo time measured using both stimulation sites (Fig. 7). The functional refractory period of the atrium was correlated with the minimal echo time measured at the near site ($r = 0.99$) and at the remote site ($r = 0.88$).

In Patients 8 to 10 the relation between the functional refractory period of the atrium and the minimal echo time could not be established. In Patient 10 the acces-

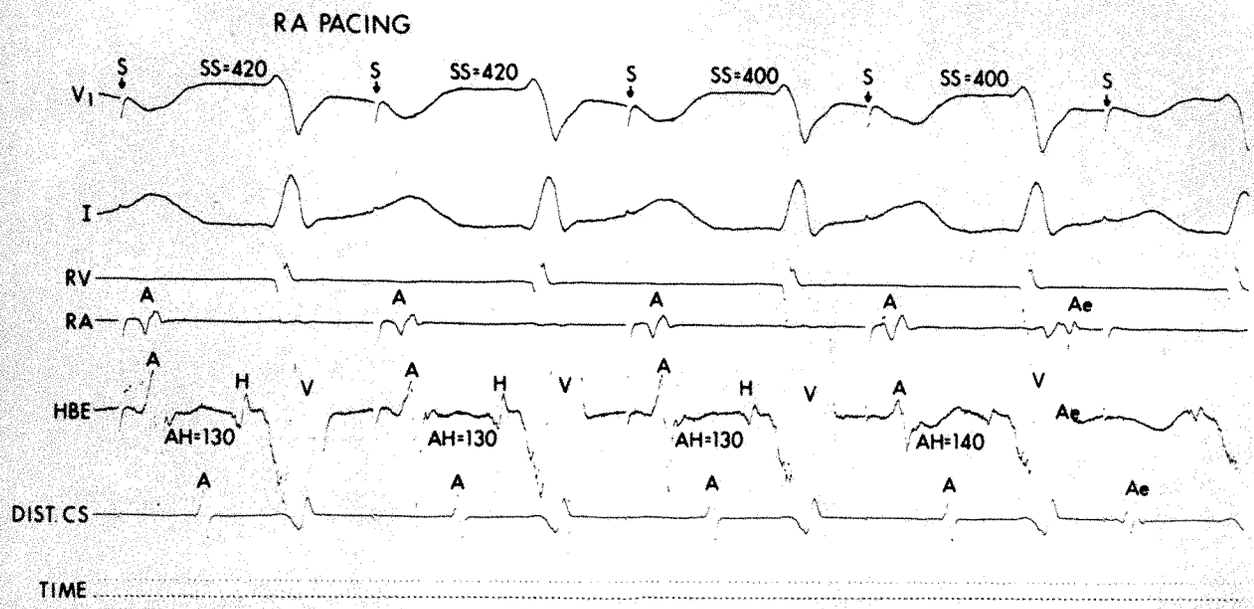


FIGURE 3. Patient 10, right atrial (RA) pacing. Tracings from above down are electrocardiographic leads V_1 and I, and electrograms from the right ventricle (RV), right atrium (RA), His bundle (HBE) and distal coronary sinus (DIST. CS). When the pacing cycle length (SS) was shortened from 420 to 400 msec, the A-H interval was prolonged from 130 to 140 msec and an atrial echo was initiated. The last stimulus shown failed to capture the atrium, which had been rendered refractory by the atrial echo indicated by A_e.

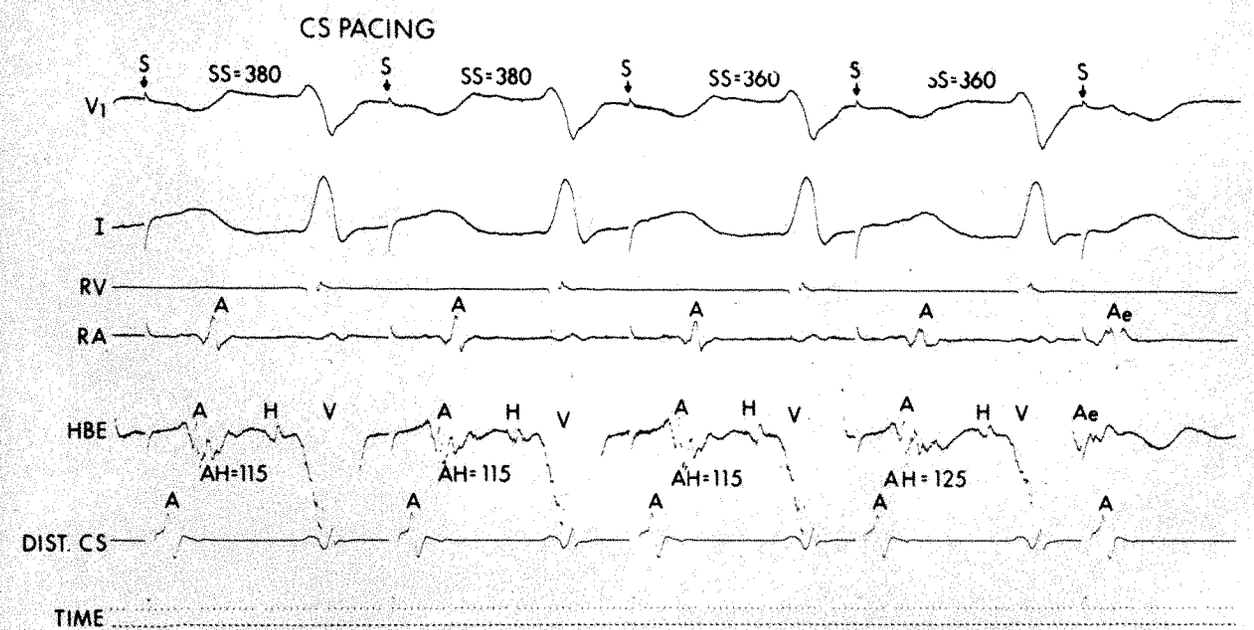


FIGURE 4. Patient 10, coronary sinus (CS) pacing. Tracings and abbreviations as in Figure 3. When the pacing cycle length (SS) was shortened from 380 to 360 msec, the A-H interval was prolonged from 115 to 125 msec. An atrial echo (A_e) was initiated. The last atrial electrograms recorded in the lower three channels indicate that atrial fusion was present. The distal coronary sinus atrial electrogram was the result of the stimulus. The atrial electrogram recorded by the catheter recording the His bundle electrogram and the atrial electrogram recorded in the right atrium occurred early and were caused by an atrial echo.

sory pathway was located in the left A-V groove, and pacing and recording near the accessory pathway were possible. The minimal echo times measured were 310 msec with stimulation in the coronary sinus and 300 msec with stimulation in the right atrium. However, the functional refractory period of the atrium was only 260 msec. In two patients the accessory pathways were located in the right A-V groove in the paraseptal regions, and stable sites for stimulation and recording near the accessory pathway were not found. Therefore the shift phenomenon could be demonstrated, but the minimal echo times were very different.

Discussion

Premature atrial stimulation has been used to study patients with a preexcitation syndrome since 1967.[3] The effect of pacing site on variables of A-V conduction has been studied and reported previously in several types of preexcitation syndromes.[2,18–20] More recently the effect of changing the stimulation site on the initiation of tachycardia by premature stimulation has been reported.[4,21–23] Studies of this effect were first reported in patients with an accessory pathway that had conduction only in the retrograde direction and that was

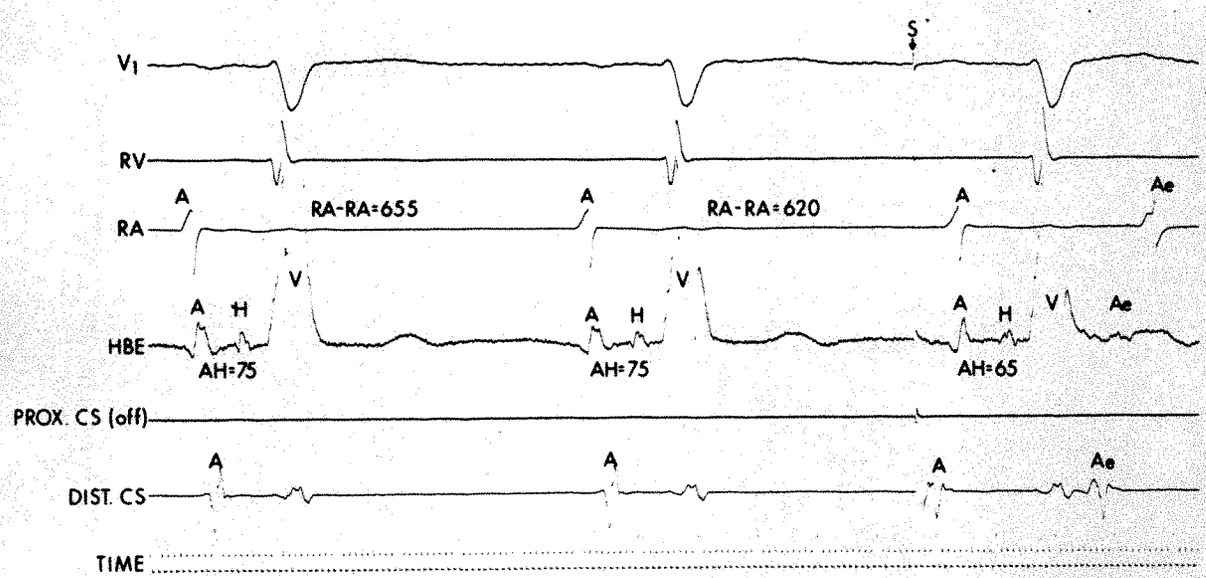


FIGURE 5. Patient 11, coronary sinus stimulation. Tracings are lead V_1 and electrograms from the right ventricle (RV), right atrium (RA), His bundle (HBE), proximal (PROX.) and distal (DIST.) coronary sinus (CS). Sinus rhythm was present with a sinus cycle length of 655 msec, and the A-H interval was 75 msec. A late diastolic stimulus (S) was applied in the coronary sinus and the RA-RA coupling interval was 620 msec. The A-H interval of the induced premature complex was 65 msec. An atrial echo was initiated in the coronary sinus. The ease with which stimuli in the coronary sinus induced atrial echoes in this patient prevented pacing in the coronary sinus.

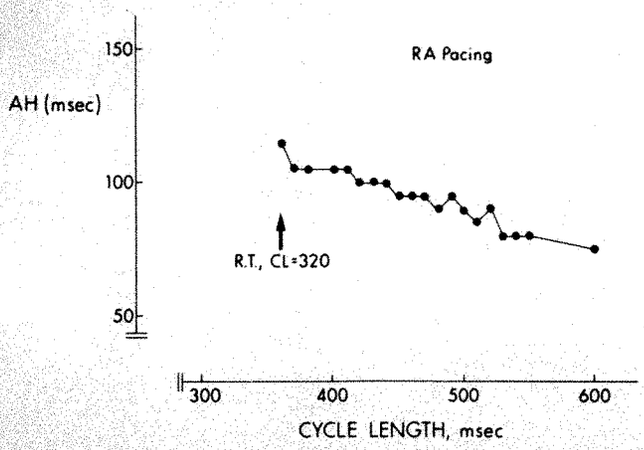


FIGURE 6. Patient 11, right atrial (RA) pacing. There was gradual prolongation of the A-H interval, and reciprocating tachycardia (R.T.) was induced at a cycle length of 360 msec. The cycle length (CL) of the tachycardia was 320 msec, indicating that Wenckebach conduction in the A-V node was not required to initiate the echo.

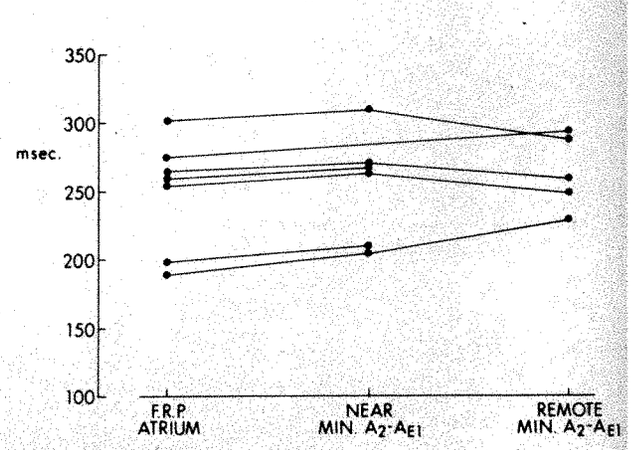


FIGURE 7. The relation between the functional refractory period (F.R.P.) of the atrium and the minimal (MIN.) echo time (A_2-A_{E1}) in seven patients (Patients 1 to 7). Both measurements were made from data recorded from a catheter positioned near the accessory pathway. These variables were closely correlated in each patient.

located in the left parietal A-V groove.[21,22] In these studies the upper limit of the echo zone was shifted to longer coupling intervals when premature stimulation in the coronary sinus was compared with premature stimulation in the right atrium. In another report 45 patients with an accessory pathway that had conduction in both the anterograde and retrograde directions were studied with the extrastimulus technique at sites in the right atrium and coronary sinus.[4] The echo zones of 3 of these 45 patients were particularly interesting because the anterograde effective refractory period of the accessory pathway was greater than the upper limit of the echo zone. In these three patients the upper limit of the echo zone was shifted to longer coupling intervals by stimulation at the site near to the accessory pathway.

Effect of changing stimulation site on initiation of atrial echoes: Our experience includes patients whose accessory pathway conducted only in the retrograde direction and patients whose accessory pathway conducted in both the anterograde and retrograde directions. In the latter group the effective refractory period of the accessory pathway exceeded the longest coupling interval that initiated an echo using at least one stimulation site. Whether conduction in the anterograde direction was present or absent, the effect of changing the site of stimulation was the same. With the extrastimulus technique, two related effects of changing the pacing site were observed. The first effect was that the upper limit of the echo zone was shifted to a longer coupling interval by pacing at the site near the accessory pathway. The second effect was that no echoes were induced during stimulation at the site remote from the accessory pathway. In patients demonstrating this latter effect, the functional refractory period of the atrium or the effective refractory period of the A-V node was achieved before any echoes were initiated. This effect indicates that failure to induce tachycardia with atrial extrastimuli during study in patients with a history of palpitations may be related to choice of stimulation site. If no tachycardia is induced with extrastimuli using one atrial site, then a second site (preferably in the opposite atrium) should be tested.

Effect of changing pacing site on initiation of atrial echoes: Information regarding the effect of changing catheter position on the initiation of echoes by atrial pacing at a fixed rate in patients with an accessory pathway was not reported in the previous studies.[4,21,22] Several phenomena related to the site of pacing were observed in our study and could be explained by the electrophysiologic characteristics of A-V nodal conduction. Patient 2 had a discontinuous curve of A-H intervals in response to atrial pacing at fixed rate with progressively shorter cycle lengths. With either pacing site A-V nodal delay was not adequate to initiate an atrial echo before the abrupt prolongation of the A-H interval occurred. This abrupt increase in A-V nodal conduction time occurred at the same cycle length with both pacing sites, and echoes were therefore first initiated at the same cycle length. In Patient 6 no atrial echoes were initiated during fixed rate pacing at either site using cycle lengths as small as 240 msec. This patient had enhanced conduction within the A-V node,[15] and conduction delay in the A-V node adequate to allow the atrium to recover simply was not achieved. In the absence of these abnormalities of conduction in the A-V node, echoes were initiated with longer cycle lengths when the pacing site was near the accessory pathway (Patients 4, 10 and 11) (Fig. 2 to 4). In Patient 10, the A-H interval recorded during fixed rate pacing in the coronary sinus was always shorter than the A-H interval recorded during fixed rate pacing of the right atrium at the same cycle length.[23] As in the patients in Group B of Batsford et al.,[23] the difference between the A-H intervals remained constant at all cycle lengths. This constant difference probably represents an artifact caused by recording a low right atrial electrogram from the catheter that records the His bundle electrogram. Patient 11 was an extreme example of the effect of pacing site on the initiation of atrial echo beats. Single stimuli applied throughout diastole in this patient initiated tachycardia (Fig. 5) when pacing of the coronary sinus was used. When pacing of the right atrium was used in Patient 11, atrial echo complexes were not initiated until a pacing cycle length of 360 msec was used (Fig. 6).

Correlation between minimal echo time and functional refractory period of right atrium: The previously reported observation[4] of the close correlation between minimal echo time and the functional refractory period of the atrium was confirmed in 7 of 10 patients in our series, and a reasonable explanation was found for the 3 exceptions. In Patients 8 and 10 the accessory pathways were located in the right paraseptal regions, and the failure to demonstrate this relation may have been related to difficulty in finding stable sites for both stimulating and recording near the accessory pathways. A catheter in the coronary sinus lies parallel to the mitral anulus and the left A-V groove. In this position electrograms from the low left atrium are recorded, and a close site can be stimulated at the same time. The local electrogram of an atrial echo initiated from an accessory pathway in the left A-V groove is recorded very early in the retrograde P wave. In contrast, right atrial recording and stimulation are performed with a catheter that is introduced into an arm or the right femoral vein and that approaches the anulus of the tricuspid valve at an oblique angle.[10] If the distal stimulating electrodes are near the anulus, then the recording electrodes are necessarily above the anulus. The local electrogram of an atrial echo initiated from an accessory pathway in the right A-V groove is recorded relatively later in the retrograde P wave. We have previously shown[4] that such recording sites that are distant from the site of the accessory pathway include large atrial contributions to the measurement of minimal echo time. In Patients 2 and 8 the disparity between the minimal echo times and the functional refractory period of the atrium may have been related to these technical considerations.

Patient 9 was the third patient in whom the functional refractory period of the atrium was not equal to

the minimal echo times. In this patient the accessory pathway was located in the left A-V groove. The minimal echo times achieved using the two pacing sites were nearly identical (310 and 300 msec), but the functional refractory period of the atrium was only 260 msec. Because the accessory pathway conducted in both the anterograde and retrograde directions, concealed penetration into the accessory pathway in the anterograde direction at some coupling intervals may have been responsible for the discrepancy between the minimal echo times and the functional refractory period of the atrium.

Clinical implication: Since the original description of the use of atrial extrastimuli in patients with the Wolff-Parkinson-White syndrome,[3] it has been hoped that serial measurements of the echo zone in these patients would provide a useful guide to drug therapy.[24–26] Our study shows that the echo zone is profoundly influenced by stimulation site and that any patient may have several echo zones. The merit of serial studies as a clinical tool can be evaluated only if the position of the catheter is well controlled.

Acknowledgment

We express our gratitude to the many cardiology fellows who participated in these studies; Laura Cook, RN and Donald Kopp, LPN, the staff of The Electrophysiology Laboratory; Jackie Kasell, electronics consultant; Don Powell and David Huggett, who prepared the illustrations; and Ann Clayton, who prepared the manuscript.

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Stress Myocardial Imaging in Mitral Leaflet Prolapse Syndrome

GEORGE J. KLEIN, MD
WILLIAM J. KOSTUK, MD, FACC
DEREK R. BOUGHNER, MD
MICHAEL J. CHAMBERLAIN, MD

London, Ontario, Canada

Mitral leaflet prolapse syndrome has been associated with anginal chest pain, atypical chest pain, electrocardiographic abnormalities and positive stress electrocardiograms. These features overlap those of ischemic heart disease. Furthermore, coronary artery disease is frequently associated with mitral leaflet prolapse. This study evaluated the usefulness of stress myocardial scintigraphy in distinguishing these two disorders. Thirty-two patients with an angiographic diagnosis of mitral leaflet prolapse were studied. Of the 22 patients (8 men and 14 women, mean age 48 years) with a normal coronary arteriogram, 5 had "typical" angina pectoris, 6 had resting electrocardiographic abnormalities and 6 had a positive stress electrocardiogram; all 22 patients had a normal stress myocardial scintigram. Of the 10 patients (7 men and 3 women, mean age 55 years) with at least 70 percent stenosis of one coronary artery, 6 had "typical" angina pectoris, 1 had resting electrocardiographic abnormalities and 7 had a positive stress electrocardiogram. Nine of these 10 patients had one or more demonstrable perfusion defects on stress myocardial scintigrams. It is concluded that mitral leaflet prolapse syndrome is not associated with regional myocardial ischemia as demonstrated with stress scintigraphy, and that stress scintigraphy, a noninvasive technique, is useful in distinguishing the mitral prolapse syndrome from mitral prolapse associated with coronary artery disease.

Idiopathic mitral leaflet prolapse syndrome occurs in approximately 6 percent of normal persons[1–3] and generally carries a benign prognosis.[1,4–6] Unfortunately, the clinical and electrocardiographic manifestations of this syndrome may mimic those of ischemic heart disease,[7–9] making differentiation by noninvasive testing difficult. Even the echocardiographic demonstration of mitral leaflet prolapse in a patient complaining of chest pain does not rule out the presence of coronary artery disease. Mitral leaflet prolapse syndrome may be a coincidental finding or may be secondary to ventricular and papillary muscle dysfunction.[4,10–13]

In patients referred for the investigation of chest pain, a careful history, physical examination, echocardiography and exercise stress testing are the standard techniques used to differentiate mitral leaflet prolapse syndrome from coronary artery disease. Echocardiography is a poor method of detecting coronary artery disease, and an exercise stress test may be abnormal in mitral leaflet prolapse syndrome despite normal coronary arteries.[8,14–17] Stress myocardial imaging with potassium-43 and thallium-201 is both sensitive and specific for the detection of regional myocardial ischemia secondary to coronary artery disease.[18–22] It is also valuable in the assessment of patients with a false positive stress electrocardiogram.[23,24] Recently, several studies[25–27] have suggested that myocardial scintigraphy may be beneficial in evaluating patients with mitral leaflet prolapse and associated coronary artery disease. We have therefore evaluated the efficacy of stress myocardial scintigrams in the noninvasive assessment of patients with mitral leaflet prolapse.

From the Cardiac Investigation Unit, University Hospital, London, Ontario, Canada. This study was supported by the Ontario Heart Foundation, Toronto, Ontario, Canada. Manuscript received December 7, 1977; revised manuscript received June 13, 1978, accepted June 14, 1978.

Address for reprints: William J. Kostuk, MD, University Hospital, P.O. Box 5339, Terminal A, London, Ontario, Canada N6A 5A5.

Methods

Patients: The records of 32 patients with angiographically proved mitral valve prolapse were examined. Left ventriculography, electrocardiography (at rest), treadmill exercise stress testing, echocardiography (28 patients), rest and stress myocardial scintigraphy and selective coronary angiography were performed in each patient.

Exercise stress testing: Maximal treadmill exercise stress testing was carried out with the patient in the fasting state, using a modified Bruce protocol with a complete 12 lead electrocardiogram recorded at 2 minute intervals during and after stress testing.[28] Exercise was continued to an end point of chest pain, severe fatigue, dyspnea, maximal heart rate or S-T segment depression. Stress electrocardiograms were considered positive for myocardial ischemia if flat or downsloping S-T segment depression of 1 mm or greater was recorded for at least 80 msec with an isoelectric S-T segment in the control tracing.

Echocardiograms: These were performed using a Unirad series C echocardiographic unit with a Honeywell model 1858 hard copy recorder. Patients were supine or inclined slightly to the left, and recordings of mitral valve motion were made in the left fourth or fifth interspace. Care was taken to avoid inferior angulation that can cause a spurious diagnosis of mitral leaflet prolapse.[29] The echocardiograms were reviewed by two of us, and recordings that disclosed mid systolic buckling or pansystolic hammocking were considered to represent mitral prolapse.[3,30,31]

Cardiac catheterization: *Left ventriculograms* were obtained in the 30° right anterior oblique and 45° left anterior oblique projections. All angiograms were reviewed by two observers. The angiographic diagnosis of mitral leaflet prolapse was based on the guidelines described by Ranganathan et al.[32,33]

Selective coronary arteriograms in multiple projections using the Judkins technique were obtained within 2 weeks of stress myocardial imaging. The coronary arteriograms were rated for luminal narrowing as normal, mild (less than 40 percent stenosis), moderate (40 to 70 percent stenosis) or severe (greater than 70 percent stenosis or occlusion). In this study, patients with at least one severe lesion were considered to have significant coronary artery disease.

Myocardial imaging: *Myocardial scans at rest* were obtained at the time of cardiac catheterization by selective injection of labeled particles of macroaggregated albumin into the coronary arteries. One hundred microcuries (mCi) of iodine-131 macroaggregated albumin consisting of 20,000 to 30,000 particles was injected into the right coronary artery, and a similar number of particles labeled with technetium-99m (200 to 300 mCi) was injected into the left coronary artery.[34] Myocardial scanning was performed in the anterior and left anterior oblique views, utilizing a rectilinear scanner. We have previously shown that scans obtained with labeled macroaggregated albumin are similar to those obtained after peripheral intravenous injection of potassium-43.[35]

Stress myocardial imaging was performed in association with the treadmill exercise test similar to the protocol described by Zaret et al.[18] At the end point of exercise (as described earlier), the radionuclide (0.5 mCi of potassium-43 or 1.5 mCi of thallium-201) was injected intravenously, and exercise was continued for an additional 45 seconds to ensure adequate myocardial uptake. Electrocardiographic monitoring was carried out throughout the test and continued for 10 minutes after exercise. Scanning was begun immediately after cessation of electrocardiographic monitoring. In the studies with potassium-43 (12 patients), images were obtained with a rectilinear scanner using a high energy medium resolution collimator and a discriminator setting of 0.3 to 0.7 kev. In four studies with thallium-201, a low energy medium resolution collimator was used with a discriminator setting of 55 to 100 kev. Scanner images were obtained in two views, anterior and left anterior oblique. The remainder of the thallium-201 studies (16 patients) were recorded with an Ohio Nuclear mobile scintillation camera using a high resolution low energy parallel hole collimator. The energy window (20 percent) of the camera was set symmetrically about 75 kev. Scintiscans were obtained in the anterior, left anterior oblique and left lateral projections.

Our rectilinear scanner is connected directly to a computer that permits a color-coded pictorial display and allows differentiation of radioactivity in the appropriate count range. Thus, the myocardial images obtained with the rectilinear scanner were interpreted utilizing the computer-processed, color-coded display. However, the scintillation camera images in this study were interpreted directly from the analog image without computer processing. The processed image in Figure 1 is for illustrative purposes only.

All scans were interpreted independently by two of us without knowledge of the clinical and coronary angiographic findings, and a consensus was obtained. Myocardial scans demonstrating a homogeneous distribution of radioactivity were interpreted as normal. A focal defect on a stress study with a similar defect in a study at rest was considered compatible with myocardial infarction; however, all patients in this study exhibited normal resting scans. Myocardial ischemia was diagnosed only if a focal defect appeared or increased in size in the stress scan compared with the scan at rest.

TABLE 1

Summary of Patient Data

	Group I	Group II
Patients (no.)	22	10
Sex	8M, 14F	7M, 3F
Age (yr)		
Range	22–61	39–70
Mean	48	55
Presenting symptom	Angina (5), atypical chest pain (15), palpitations (2)	Angina (6), atypical chest pain (2), positive ex ECG (1), TIA (1)
Auscultation	Click or murmur, or both (19)	Click or murmur, or both (5)
Resting ECG	ST-T changes (6), normal (16)	ST-T changes (1), normal (9)
Stress ECG	Positive (6), borderline (5), normal (11)	Positive (7), borderline (1), normal (2)
Echocardiogram	Diagnostic (18), equivocal (1), tech poor (2), normal (1)	Diagnostic (5), tech poor (1), normal (2), NP (2)
Stress myocardial scan	Normal (22) (^{43}K [8], ^{201}Tl [14])	Normal (1), abnormal (9) (^{43}K [4] ^{201}Tl [6])

Group I = patients with mitral leaflet prolapse and normal coronary arteries; Group II = patients with mitral leaflet prolapse and significant coronary artery disease.

Numbers in parentheses or brackets indicate number of patients.

ECG = electrocardiogram; ex = exercise; ^{43}K = potassium-43; NP = not performed; tech = technically; TIA = transient ischemic attacks; ^{201}Tl = thallium-201.

Results

Clinical features: On the basis of the selective coronary arteriograms, the patients with mitral leaflet prolapse were classified into two groups (Table I). Group I consisted of 22 patients (8 men and 14 women, mean age 48 years) with mitral leaflet prolapse and normal coronary angiograms; one patient in this group had an associated secundum atrial septal defect. Group II consisted of 10 patients (7 men and 3 women, mean age 55 years) with mitral leaflet prolapse and significant coronary artery disease involving at least one major vessel.

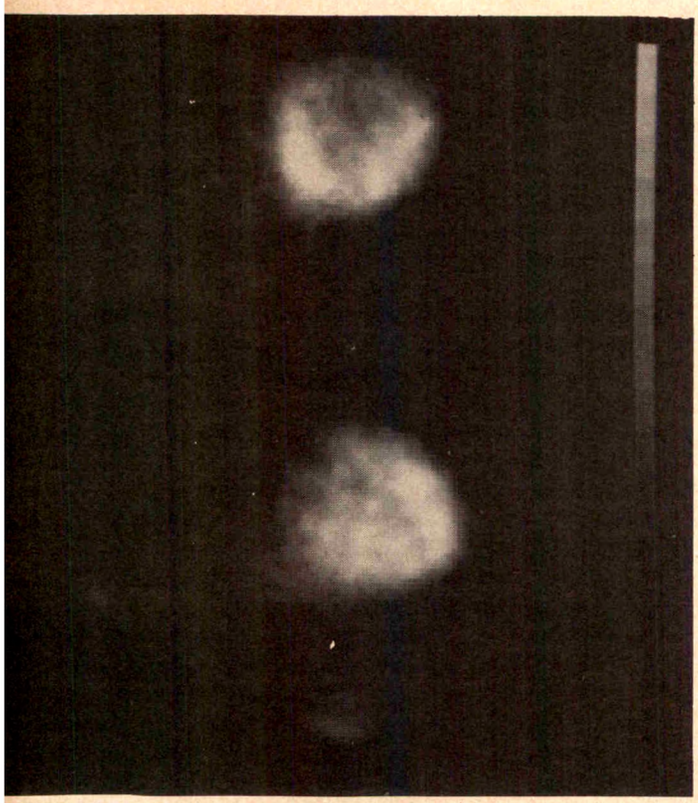
No patient in either group had historical, electrocardiographic or scintigraphic evidence of previous myocardial infarction. In both groups, the most common presenting complaint was chest pain. Twenty patients in group I presented with chest pain; 5 patients had typical angina pectoris, defined as exertional chest discomfort that was readily relieved by rest or nitroglycerin, or both. Fifteen patients had atypical chest pain. The other two patients in group I presented with palpitations due to cardiac arrhythmia. Of the eight patients in group II presenting with chest pain, six had typical angina pectoris and two had atypical pain. Of the remaining patients in group II, one was being investigated for transient ischemic attacks and the other for a strongly positive exercise test.

Electrocardiography: The resting electrocardiogram was abnormal in six patients in group I. The most common abnormality was S-T segment flattening with flat to inverted T waves in the inferolateral leads. In group II, one patient had slight S-T segment depression in the inferolateral leads, and nine patients had a normal resting electrocardiogram.

Maximal treadmill exercise stress testing was positive in six patients (27 percent) in group I and seven patients (70 percent) in group II. Five patients in group I and one in group II had a borderline response (S-T depression less than 1 mm) after exercise. The remaining patients (11 in group I and 2 in group II) had a normal electrocardiographic response to exercise.

Echocardiography: Echocardiographic changes compatible with the diagnosis of mitral leaflet prolapse were demonstrated in 18 patients (82 percent) in Group I and 5 patients (63 percent) in group II. (Echocardiography was not performed in two patients.)

Myocardial imaging: In all patients in both groups, the resting myocardial perfusion scans obtained after the direct intracoronary injection of labeled macroaggregated albumin particles at selective coronary angiography were normal. After exercise stress, none of the patients in group I had a perfusion defect (Fig. 1). However, in group II 9 of the 10 patients developed perfusion defects on the stress myocardial scan (Fig. 2).



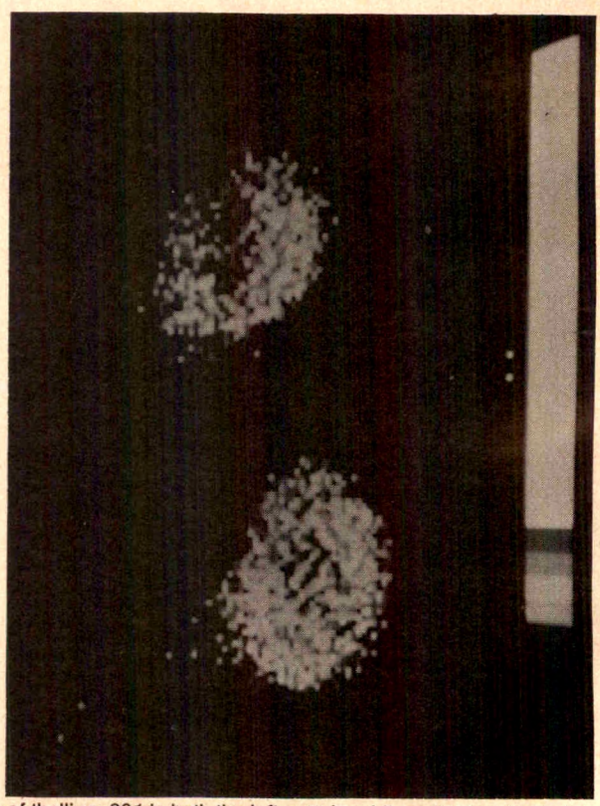


FIGURE 1 (left). Exercise myocardial scans showing normal homogeneous uptake of thallium-201 in both the left anterior oblique (**top**) and anterior (**bottom**) views. The scans were obtained with a gamma camera and the images were processed by computer. In this patient the stress electrocardiogram was positive for ischemia with horizontal S-T segment depression of 1.5 mm in leads II, III, aVF and V_6. Subsequent coronary angiograms were normal.

FIGURE 2 (right). Thallium-201 exercise myocardial scan obtained with a rectilinear scanner. An anterior perfusion defect appears clearly in the left anterior oblique view (**top**) and less clearly in the anterior view (**bottom**). The stress electrocardiogram was positive with S-T segment depression of 1.5 mm in leads V_1 to V_3. Coronary angiography revealed disease of both the left anterior descending and right coronary arteries.

Discussion

The diagnosis of coronary artery disease in the presence of mitral leaflet prolapse may be difficult. Chest pain in patients with the mitral leaflet prolapse syndrome may be mistaken for angina pectoris due to coronary artery disease.[7–9] Resting electrocardiographic abnormalities in the syndrome may suggest myocardial ischemia, and Q waves may occasionally be present.[15,36,37] Positive treadmill exercise electrocardiograms[8,14–17] and ventricular arrhythmias[14,38,39] are well known features of the syndrome. Both coronary artery disease and mitral leaflet prolapse syndrome are common disorders, and the simultaneous occurrence of both would not be unexpected.[13] In the presence of coronary artery disease, mitral leaflet prolapse may result from ventricular contraction abnormalities or papillary muscle dysfunction.[10,12,40,41]

Stress myocardial imaging with potassium-43 and thallium-201 has been shown to be a sensitive and specific indicator of regional myocardial ischemia caused by coronary artery disease.[18–22] The uptake of radioactive tracer in normal myocardium depends mainly on adequate coronary blood flow and the integrity of cell membrane adenosine triphosphatase, which regulates the transmembrane electromechanical gradient of sodium and potassium.[18,22,42] Regions of myocardium rendered ischemic during stress testing take up less tracer, and subsequent scanning demonstrates perfusion defects in the appropriate area.[18,20,22] At present, myocardial imaging is a quantitative study that depends on the visualization of relative differences in radionuclide uptake. False negative studies occur occasionally, most commonly in patients with single vessel disease (especially in the right coronary artery) and an area of regional myocardial ischemia too small to be visualized with current scanning techniques. The smallest defect that can confidently be detected with thallium scintigraphy is equivalent to an area of myocardium with a mass of 6 g and a 40 percent decrease in perfusion compared with normal myocardium.[43] Furthermore, small lesions are best defined when seen from either a front or a tangential view.[44] False negative studies have also occurred occasionally in patients with extensive triple vessel disease and diffuse global myocardial ischemia that has resulted in a homogeneous normal distribution of radionuclide.

Role of myocardial imaging in patients with mitral valve prolapse: We have found stress myocardial imaging to be a helpful noninvasive technique for differentiating patients with mitral leaflet prolapse syndrome from those with mitral leaflet prolapse associated with coronary artery disease. In this study, all patients with mitral leaflet prolapse syndrome and normal coronary arteries had normal stress myocardial scans indicating that regional myocardial perfusion, as demonstrated with this technique, was normal on exercise. In contrast, 9 of the 10 patients with significant coronary artery disease and prolapse had perfusion defects on exercise. In one patient with triple vessel disease, the myocardial scan with potassium-43 was normal. Our results are comparable with those of Gaffney et al.,[26] who reported normal exercise myocardial scans in 12 patients with mitral valve prolapse and presumed normal coronary arteries (only 4 of their patients underwent cardiac catheterization). Similarly, Massie et al.[27] found normal exercise scans in 19 patients with mitral leaflet prolapse and normal coronary arteries proved by angiography; they found perfusion defects in 6 patients with associated coronary artery disease. The results of these three studies contradict those reported in three recent abstracts[45–47] indicating that stress myocardial perfusion scintigrams did show perfusion defects in some patients with mitral prolapse syndrome. The abstracts do not indicate the reasons for the discrepancy.

Causes of chest pain and abnormal electrocardiogram in mitral valve prolapse—the role of ischemia: A popular theory to explain the chest pain and the electrocardiographic abnormalities in patients with the mitral leaflet prolapse syndrome postulates the presence of ischemia in the posterior papillary muscle and adjacent ventricle.[10,36,48] This theory suggests that increased stress on the chordae tendineae in mitral leaflet prolapse produces a chronic overload of the posterior papillary muscle and that the somewhat precarious blood supply[49] may cause ischemia in this area. However, there are several problems with this theory. Increased myocardial lactate production has not been consistently demonstrated,[50–52] and a good correlation between clinical symptoms, ventricular contraction abnormalities and degree of prolapse has not been observed.[50] Clinical observation shows that the pain of mitral prolapse is usually unrelated to exertion, although this should produce increased myocardial oxygen demand and increased chordal stress due to greater ventricular emptying. Our findings of normal myocardial perfusion both at rest and during exercise in patients with mitral leaflet prolapse alone but not in patients with associated coronary artery disease create further doubt about whether the chest pain in the mitral prolapse syndrome is ischemic in nature. However, generalized myocardial ischemia or very small regions of ischemia can be missed by present scanning techniques.

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Noninvasive Assessment of Coronary Stenoses by Myocardial Imaging During Pharmacologic Coronary Vasodilatation. III. Clinical Trial

PETER C. ALBRO, MD
K. LANCE GOULD, MD, FACC
R. JEFFREY WESTCOTT, MD
GLEN W. HAMILTON, MD
JAMES L. RITCHIE, MD
DAVID L. WILLIAMS, PhD

Seattle, Washington

Thallium-201 myocardial imaging was performed at rest, after maxima treadmill exercise and during coronary vasodilatation induced by the in travenous administration of dipyridamole in 62 patients undergoing cor onary angiography. Myocardial images after dipyridamole infusion were compared with rest and exercise thallium-201 images to determine the utility of pharmacologic stress for detecting coronary artery disease. Dipyridamole, 0.142 mg/min, was infused for 4 minutes with electrocar diographic and blood pressure monitoring, and thallium-201 was injected intravenously 4 minutes after infusion.

Myocardial/background count ratios of 2.3 ± 0.5 (mean ± 1 standard deviation) after the administration of dipyridamole were higher than simila ratios for exercise images (2.1 ± 0.5; $P < 0.001$). The sensitivity of thal lium-201 imaging for detecting significant coronary artery disease was equal for dipyridamole and exercise stress. In 51 patients with a 50 percent or greater stenosis of one or more coronary arteries, image defects were identified in 34 of 51 (67 percent) exercise and dipyridamole images. Twenty of 51 patients (39 percent) had abnormal rest images; in 17 of 20 patients, new or increased image defects were present after exercise and the infusion of dipyridamole. One of 11 patients (9 percent) with no stenosis of 50 percent or greater had a defect on exercise and dipyrida mole images. Six of seven patients with new or enlarged image defects after the intravenous administration of dipyridamole also had new or en larged defects after the oral administration of dipyridamole.

After the infusion of dipyridamole, the heart rate increased from 64 ± 10 beats/min supine to 88 ± 13 beats/min standing ($P < 0.001$), and blood pressure decreased from 129 ± 16/80 ± 9 to 120 ± 17/75 ± 9 mm Hg ($P < 0.001$). Angina and S-T depression occurred more frequently with exercise than with dipyridamole. S-T depression occurred in only two patients (3 percent) with dipyridamole, suggesting that diagnostic images were often obtained without significant ischemia. This study demonstrates that pharmacologic coronary vasodilatation is as effective as maxima treadmill exercise in creating myocardial perfusion abnormalities de tectable with thallium-201 imaging in man.

Previous studies have demonstrated the feasibility of identifying coro nary arterial stenosis with thallium myocardial imaging during phar macologic coronary vasodilatation in animals[1,2] and man.[3] This repor compares the clinical diagnostic sensitivity and specificity of thalliur myocardial imaging after coronary vasodilatation induced by intravenou dipyridamole with those of thallium imaging after treadmill exercis stress.

From the Seattle Veterans Administration Hospital and Department of Medicine, University of Washington, Seattle, Washington. This study was supported by Veterans Administration General Medical Research, Seattle, Washington, by Grant-in-Aid 63-2749 and Research Training Fellowships (Drs. Westcott and Albro,) from the Washington State Heart Association, Seattle, Washington and by Grants HL 18492-01, -02 and -03 from the National Institutes of Health, Bethesda, Maryland. Manuscript received March 21, 1978; revised manuscript received June 20, 1978, accepted July 5, 1978.

Address for reprints: K. Lance Gould, MD, Seattle Veterans Administration Hospital, 4435 Beacon Avenue South, Seattle, Washington 98108.

Methods

Patients: Sixty-two patients undergoing coronary arteriography and exercise stress testing for suspected coronary artery disease were studied. All patients were hospitalized for clinical evaluation including history, physical examination, routine laboratory tests, electrocardiogram and chest X-ray film. Most patients had an initial treadmill stress test using the Bruce protocol.[4] Diagnostic coronary arteriography was performed using the Judkins femoral arterial or the Sones brachial arterial approach, and 35 mm cineangiograms of the left ventricle and coronary arteries were obtained in multiple views. After discussion with each patient, written informed consent was obtained for exercise testing, for injection of thallium-201 for myocardial imaging and for the administration of intravenous dipyridamole. Myocardial images were obtained at rest, during maximal treadmill exercise and after the intravenous administration of dipyridamole.

Myocardial imaging: *For resting studies,* patients were injected with 1.5 to 2.0 mCi of thallium-201 while standing. Thirty minutes later myocardial images were obtained in the anterior; 30°, 45° and 60° left anterior oblique; and left lateral views. Patients were supine, and the gamma camera was rotated from 0° to 60° during all imaging studies. Imaging was performed using an Ohio Nuclear series 100 gamma camera equipped with a high resolution, low energy collimator. Images were recorded on Polaroid® film and collected by a Nova II miniprocessor adapted for use in nuclear medicine (Medical Data Systems, Ann Arbor, Michigan) with a 128 by 128 display, dual disc drive, magnetic tape storage and software for localizing areas of interest by light pen for analysis of activity.

One week later, after residual thallium-201 activity was no longer detectable in the heart, maximal treadmill exercise testing was performed according to the Bruce protocol, and thallium-201 was injected 1 minute before the completion of exercise. Patients who had not completed stage I on previous treadmill testing began exercise in a substage (1.7 miles/hour, 0 to 5° grade) to ensure completion of 3 minutes of exercise stress before the injection of thallium-201. As soon as possible after exercise and within 10 minutes in most patients, imaging was started. Images were obtained in the same five views, beginning with the 45° left anterior oblique view.

At least 1 week later, myocardial images were again obtained after the injection of thallium-201 during coronary vasodilatation induced by the intravenous administration of dipyridamole. A 19 gauge butterfly needle was placed in a large forearm or antecubital vein. A baseline electrocardiogram and blood pressure measurements were obtained and modified precordial electrode leads attached as in exercise testing. With the patient supine, dipyridamole (Boehringer Ingelheim, Elmsford, New York) was infused intravenously at a rate of 0.142 mg/kg per min for 4 minutes (total dose 0.568 mg/kg) using a Harvard model 551 infusion pump modified by insertion of a 10-turn potentiometer for more exact regulation of the infusion rate. Continuous electrocardiographic monitoring was performed during and for 10 minutes after the infusion, and blood pressure and heart rate were recorded at 1 minute intervals. Four minutes after the infusion, the patient stood up and walked in place, and 1.5 to 2.0 mCi of thallium-201 was injected 5 to 5 1/2 minutes after the infusion. The patient continued to walk slowly in place for 5 minutes after the injection of thallium. Myocardial images were then obtained in the five standard views.

Five patients were given a second infusion of dipyridamole, for a total dose of 0.757 mg/kg. These patients were selected and studied with use of the following criteria: (1) The patient was known to have normal or near normal left ventricular function, (2) supine heart rate increased to a maximum of less than 130 percent of control heart rate in the 4 minutes after the initial infusion of dipyridamole, and (3) no angina pectoris occurred with the initial infusion. Four minutes after the initial infusion, a second infusion of 0.142 mg/kg per min was administered for 1.33 minutes. Two minutes after this infusion, the patient stood up and walked in place; thallium was injected 1 minute later. Myocardial imaging was performed only after the second infusion in these patients.

Ten patients also underwent myocardial imaging after the oral administration of dipyridamole. Dipyridamole, 200 mg (five patients) or 300 mg (five patients) in crushed tablets suspended in corn syrup extract, was administered to patients in the fasting state. Supine and standing blood pressure, electrocardiogram and symptoms were recorded before and every 15 minutes after the ingestion of dipyridamole. Thallium was injected 45 minutes after the ingestion of dipyridamole, and myocardial images were obtained 15 minutes after the injection of thallium.

Analysis of coronary arteriograms: Coronary stenoses were measured by manually tracing the coronary arteries from projected 35 mm cineangiographic frames showing the most severe stenosis in each view. The normal diameter minus the diameter of the stenosis was divided by the normal diameter of an apparently normal adjacent area of the same artery to determine the percent diameter stenosis. A patient was considered to have significant coronary disease if one or more coronary stenoses were 50 percent or greater. Left ventricular volumes were calculated from single plane cineangiograms using the area-length method of Dodge adapted for the 30° right anterior oblique projection.

Ejection fraction was calculated from the formula:

$$\text{ejection fraction} = \frac{\text{end-diastolic volume} - \text{end-systolic volume}}{\text{end-diastolic volume}}$$

Clinical analysis of thallium images and exercise electrocardiography: Three experienced observers independently read the original Polaroid photographs of myocardial perfusion images without knowing the patient's name, the diagnosis or the type of stress. No background subtraction was performed. Exercise and dipyridamole images were identified only as "stress" studies and were read individually and compared with the resting images for the patient. Differences in interpretation were resolved by a consensus reading of three observers.

The sensitivity (true positives/true positives plus false negatives) and specificity (true negatives/true negatives plus false positives) of each test in identifying patients with one or more coronary stenoses of 50 percent or more were calculated for the electrocardiogram at rest, exercise S-T depression, resting thallium-201 images, exercise images and dipyridamole images. Electrocardiographic Q waves at rest (0.04 second or longer in duration, 25 percent or more of total QRS amplitude in same lead) or S-T depression during or after exercise (1 mm or more of horizontal or downsloping S-T depression 0.06 second after the QRS complex) were criteria for positive electrocardiographic results. Sensitivity and specificity were calculated for combined resting-exercise electrocardiography and resting-exercise imaging.

The overall accuracy of resting and stress thallium imaging alone and thallium imaging plus resting and exercise electrocardiography for detecting significant coronary stenoses was analyzed according to Bayes's theorem.[5–7] The post-test probability of correctly categorizing an anatomically normal or abnormal patient on the basis of an abnormal or normal test result was calculated for a theoretical prevalence rate (pretest

probability) of disease ranging from 0 (no disease) to 100 percent (all members of group with disease).

Post-test probability of having disease with a positive test was defined as the number of true positives divided by the total number of positive tests, where a true positive was defined as an abnormal image and 50 percent or greater diameter coronary stenosis as assessed with arteriography. For any prevalence of disease, the post-test probability of having disease with an abnormal image was calculated as

$$\frac{\text{(sensitivity)(prevalence)}}{\text{(sensitivity)(prevalence)} + \text{(1.0 - specificity)(1.0 - prevalence)}}$$

or

$$\frac{\text{true positives}}{\text{true positives + false positives}}$$

Post-test probability of having disease with a normal or negative test was defined as the number of false negatives divided by all negative tests, where a false negative result was an arteriogram showing 50 percent or greater diameter coronary stenosis with a normal test. Post-test probability of disease with a normal test was calculated for each prevalence as

$$\frac{\text{(1.0 - sensitivity) (prevalence)}}{\text{(1.0 - sensitivity) (prevalence) + (specificity) (1.0 - prevalence)}}$$

or

$$\frac{\text{false negatives}}{\text{false negatives + true negatives}}$$

Computer analysis of thallium images: Resting and stress thallium images were analyzed quantitatively by computer as follows: A single 9 point smooth of each image was carried out. The resting control myocardial image, in most cases the 45° left anterior oblique view, was displayed on a persistence oscilloscope and the heart outlined by light pen. Two specific areas that appeared to represent average background were outlined lateral and superior to the myocardial region of interest as previously described.[3] A computer program was developed to translate areas of interest in the resting image until they could be visually superimposed on the corresponding exercise or dipyridamole image, so that areas of interest were identical for each study of the patient. The activity counted in each area of interest was normalized for the injected thallium dose in millicuries, the duration of imaging in seconds and the number of channels in the area of interest. Units of activity were then expressed as counts/sec per channel per millicurie injected. Myocardial and background counts for exercise and dipyridamole images were compared with resting values using the paired t test for differences and expressed as percent of corresponding values of the resting image for graphic display.

Myocardial uptake and image quality were assessed quantitatively by calculating the ratio of myocardial activity to the average activity of the two background areas for each image. Myocardial to background count ratios calculated from exercise and dipyridamole images were expressed as percent of control values at rest. Patients were then ranked from the patient having the largest percent increase in myocardial to background count ratio after dipyridamole to the patient having the largest percent decrease in this ratio. The patients ranked by percent change in myocardial to background count ratio were classified into four groups with an equal number of patients in each group. The group with the largest increase in ratio was compared with each of the other groups by the unpaired t test for changes in heart rate and blood pressure with dipyridamole, left ventricular ejection fraction, use of propranolol and sensitivity of thallium-201 imaging. The groups were also compared for the severity of exercise limitation as determined with functional aerobic impairment and the product of maximal blood pressure and heart rate during exercise.

To analyze the effects of exercise on myocardial/background (M/B) ratios, patients were also ranked from the largest percent increase in this ratio with exercise to the largest percent decrease and classified into four groups with an equal number of patients in each group. The first group was compared with each of the other groups using the unpaired t test for the following variables: maximal heart rate during exercise, maximal blood pressure times heart rate, functional aerobic impairment, ejection fraction and percent change in M/B ratio from resting to dipyridamole image.

Blood pressure and heart rate changes with dipyridamole: Blood pressure and heart rate after dipyridamole in the standing position were compared with supine control values by paired t testing to assess the systemic effects of dipyridamole infusion.

Occurrence of myocardial ischemia: The occurrence of angina pectoris or S-T depression, or both, with exercise was compared with that after dipyridamole in the entire group of

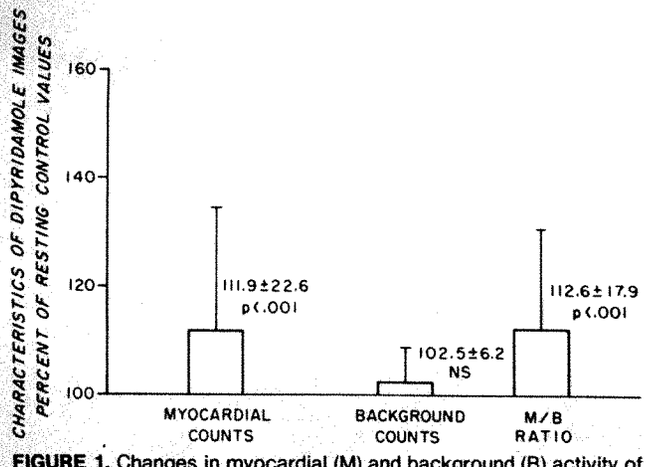


FIGURE 1. Changes in myocardial (M) and background (B) activity of dipyridamole thallium images expressed as a percent of control resting values. **Bars** indicate 1 standard deviation. Probability (p) values are shown according to a paired t test comparing dipyridamole and resting values for each patient. NS = not significant.

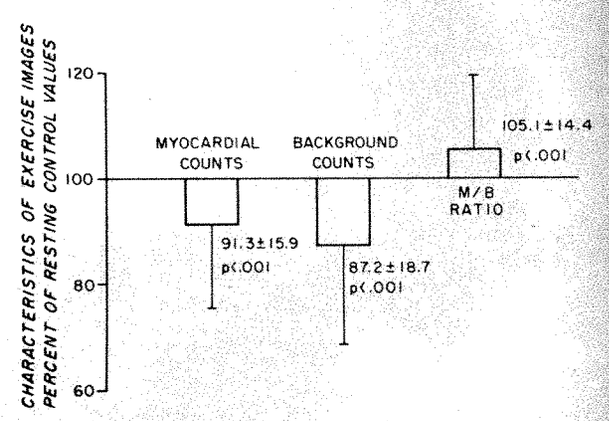


FIGURE 2. Changes in myocardial and background activity of exercise thallium images expressed as a percent of control resting values. p = probability.

TABLE I

Abnormal Exercise and Dipyridamole Thallium-201 Images

Coronary Stenosis on Arteriography	Rest	Exercise	Dipyridamole
≥50 percent	20 of 51 (39%)	34 of 51 (67%)	34 of 51 (67%)
<50 percent	0 of 11 (0%)	1 of 11 (9%)	1 of 11 (9%)

patients and in the subset of patients with abnormal images. The significance of differences in the prevalence of angina or S-T depression, or both, with each test was determined with chi square analysis.

Results

Myocardial uptake of thallium after exercise and dipyridamole compared with rest (Fig. 1 and 2): Myocardial counts/sec per dose per channel increased significantly in dipyridamole images to 111.9 ± 22.6 percent (mean ± 1 standard deviation) of resting counts (P <0.001); background counts increased insignificantly to 102.5 ± 6.2 percent of resting counts. Myocardial counts in exercise images decreased significantly to 91.3 ± 15.9 percent of resting counts (P <0.001), and background counts showed a larger decrease to 87.2 ± 18.7 percent of resting values (P <0.001). Myocardial to background (M/B) ratios increased slightly but significantly from resting to exercise images. The mean M/B ratio was 2.0 ± 0.3 (standard deviation, with standard error of the mean 0.04) at rest and 2.1 ± 0.5 (standard deviation, with standard error of the mean 0.06) with exercise; this difference was significant (P <0.006 by paired t testing). The mean M/B ratio for dipyridamole images was 2.3 ± 0.5 (standard deviation, with standard error of the mean 0.07), significantly higher than for resting or exercise images by paired t testing (P <0.001). There was considerable individual variation in M/B ratio, with overlap of the resting and stress image values between groups. Thus, the image quality of thallium-201, as reflected in myocardial to background ratio, improved for both exercise and dipyridamole, but by different mechanisms. With exercise, background activity showed a larger decrease than myocardial activity, and the M/B ratio increased. After the administration of dipyridamole, myocardial activity increased but background activity did not change, thereby also causing an increased M/B ratio.

Clinical reading of thallium images (Table I): Of 51 patients with a 50 percent or greater diameter stenosis of one or more coronary arteries, 20 patients (39 percent) had perfusion defects in images at rest. Thirty-four patients (67 percent) had perfusion defects after exercise stress, and 34 patients (67 percent) had image defects after the administration of dipyridamole. Thus, thallium-201 imaging during dipyridamole-induced coronary vasodilatation was equal in sensitivity to thallium-201 imaging with maximal exercise testing. Seventeen of 20 patients with resting image defects had new or enlarged defects after the administration of dipyridamole and after exercise stress. Fourteen patients with normal images at rest had image defects after the administration of dipyridamole and after exercise. In every patient with abnormal images and coronary artery disease, defects in images at rest or during stress corresponded to myocardium supplied by a stenotic or occluded coronary artery.

One of 11 patients with insignificant coronary disease on angiography had a defect in both exercise and dipyridamole images. This patient had a 40 percent stenosis of the proximal right coronary artery and an inferior defect after exercise and the administration of dipyridamole. He also had angina and S-T depression during treadmill exercise. Therefore, these results may be considered false positive by our criteria because the coronary lesion was underestimated with angiography. One patient with a 60 percent stenosis of the anterior descending coronary artery had an anterior defect after the administration of dipyridamole and no defect with exercise. Another patient with an occluded right coronary artery had an inferior defect in exercise images; his dipyridamole images were considered equivocal but probably normal.

For each patient the exercise or dipyridamole images were visually compared for relative diagnostic quality. Diagnostic quality was assessed by visually comparing the size, number and clarity of new or enlarged defects for blinded exercise versus dipyridamole images. In 15 patients, the dipyridamole image was judged to contain more diagnostic information, and in 13 the exercise image; in the remaining 34 patients the exercise and dipyridamole images were rated equal in diagnostic information.

TABLE II

Thallium-201 Imaging and Electrocardiography in Diagnosis of Greater Than 50 Percent Stenosis

Test	Sensitivity	Specificity
Resting ECG (Q waves)	23 of 51 (45%)	11 of 11 (100%)
Exercise S-T depression	21 of 51 (41%)	8 of 11 (73%)
Thallium-201 defect		
At rest	20 of 51 (39%)	11 of 11 (100%)
With exercise	34 of 51 (67%)	10 of 11 (91%)
With dipyridamole	34 of 51 (67%)	10 of 11 (91%)
Combined ECG and thallium-201 imaging	43 of 51 (84%)	8 of 11 (73%)

ECG = electrocardiogram.

Sensitivity and specificity of electrocardiographic and thallium-201 imaging in assessing coronary stenoses (Table II): Electrocardiography at rest, exercise S-T monitoring and myocardial imaging at rest each identified a minority of patients with coronary stenoses of 50 percent or greater diameter narrowing. Exercise or dipyridamole imaging was the most sensitive single test (67 percent) and was specific (91 percent). Combined resting and exercise electrocardiography had a sensitivity of 75 percent but a specificity of only 73 percent. Resting and exercise electrocardiography combined with resting and exercise myocardial imaging had a sensitivity of 84 percent and a specificity of 73 percent. Three patients had diagnostic S-T depression on exercise testing but no significant coronary stenoses. One of these three had angina during exercise, an abnormal dipyridamole and exercise image and a 40

percent coronary stenosis that was probably underestimated with angiography, as indicated earlier.

Hemodynamic effects of dipyridamole infusion (Table III): Compared with supine control values, blood pressure and heart rate changed significantly after the infusion of dipyridamole and when the patient stood up before the injection of thallium-201. Heart rate increased; systolic and diastolic blood pressure decreased slightly. Maximal supine heart rate occurred 2 to 3 1/2 minutes after the end of the dipyridamole infusion in most patients. To avoid postural symptoms, patients were instructed to walk in place immediately after standing. After standing, two patients described mild lightheadedness that cleared while the patient walked in place; neither patient was hypotensive. It was not necessary to interrupt the infusion of dipyridamole in any patient because of symptoms or hemodynamic changes. No patient had ventricular arrhythmias or hypotension with this dose regimen, although we previously reported orthostatic hypotension in one patient who received a bolus injection of 0.57 mg of intravenous dipyridamole.[3]

Myocardial counts/background counts after the administration of dipyridamole compared with hemodynamic changes, left ventricular function, severity of exercise stress, sensitivity of myocardial imaging and use of propranolol (Table IV): Patients were ranked from the patient with the highest percent increase in myocardial/background (M/B) ratio after the administration of dipyridamole to the patient with the highest percent decrease in this ratio and classified into four groups with an equal number of patients in each group. Patients in the first group had a 35.5 percent increase in the M/B ratio, patients in the second group had a 15.3 percent increase, and so on. Patients with larger increments in the M/B ratio also had larger increments in heart rate after the administration of dipyridamole, suggesting individual variation in the drug's effects for an equivalent dose per body weight. Differences in percent increase in heart rate were significant between the first group and the other three groups, but otherwise were not significant.

There was a small but significant decrease in systolic blood pressure for the entire study group, but the blood pressure response to dipyridamole did not differ significantly among groups. Left ventricular ejection fraction varied markedly among patients in each group and was significantly lower only in the fourth group. The maximal pressure-rate product (blood pressure × heart rate ÷ 100) during exercise, which correlates with maximal oxygen consumption and severity of exercise stress, was abnormally low in all groups, and there was no significant difference among groups. A majority of patients in each group were taking propranolol (differences among groups not significant). Forty of 51 patients with significant coronary stenoses were taking propranolol; 25 of these 40 patients (63 percent) had image defects after the administration of propranolol. Eleven of 51 patients with coronary stenoses were not taking propranolol, and 9 of these 11 patients (82 percent) had image defects. The sensitivity of thallium-201 imaging was not significantly different in patients who were and were not taking propranolol.

Change in the myocardial to background ratio of images at rest compared with dipyridamole images was a useful index of image quality and correlated roughly with increased pharmacologic response as reflected by mean percent changes in heart rate. Therefore, we expected to find a decreased diagnostic sensitivity in group 4 (patients whose M/B ratio did not increase after the administration of dipyridamole). However, 12 of 14 patients (86 percent) with 50 percent or greater coronary stenosis in group 4 had image defects with di-

TABLE III

Heart Rate and Blood Pressure Responses to Dipyridamole (0.142 mg/kg per min for 4 minutes)

	Control	Dipyridamole and Standing
Heart rate (beats/min)	64 ± 10	88 ± 13*
Blood pressure (mm Hg)		
Systolic	129 ± 16	120 ± 17*
Diastolic	80 ± 9	75 ± 9*

* $P < 0.001$ by paired t test.
Values expressed as mean ±1 standard deviation.

TABLE IV

Changes in Myocardial/Background (M/B) Ratios With Dipyridamole

Group	M/B Dipyr / M/B Rest	% Δ HR Supine	% Δ HR	% Δ SBP	Ejection Fraction (%)	FAI (%)	Maximal Exercise PRP	Sensitivity no.	Sensitivity %	Patients Receiving Propranolol no.	Patients Receiving Propranolol %
1	1.355 ± 0.090	40 ± 14	50 ± 10	−7 ± 8	64 ± 9	31 ± 22	201 ± 82	7 of 10	70	11 of 15	73
2	1.153 ± 0.048*	25 ± 10 $P < 0.002$	37 ± 9* NS	−7 ± 7 NS	60 ± 14 NS	31 ± 18 NS	204 ± 71 NS	8 of 11	73	8 of 15	53
3	1.051 ± 0.020*	23 ± 11*	33 ± 14*	−6 ± 7 NS	57 ± 17 NS	37 ± 26 NS	214 ± 69 NS	5 of 14	36	15 of 15	100
4	0.928 ± 0.075*	22 ± 11*	32 ± 16*	−4 ± 11 NS	53 ± 15 $P < 0.05$	38 ± 18 NS	187 ± 49 NS	12 of 14	86	11 of 16	69

* Probability (P) < 0.001 by unpaired t test of group compared with group 1.
Dipyr = dipyridamole; FAI = percent functional aerobic impairment; NS = not significant; % Δ HR = change in heart rate, control supine to standing after infusion of dipyridamole; % Δ SBP = change in systolic blood pressure, control supine to standing after infusion of dipyridamole; PRP = blood pressure × heart rate ÷ 100; sensitivity = number of patients with dipyridamole image defects ÷ number of patients with 50 percent or greater stenosis.

TABLE V

Changes in Myocardial/Background (M/B) Ratios With Exercise

Group	M/B Exer / M/B Rest	Max HR	Max PRP	% Δ PRP	FAI (%)	M/B Dipyr / M/B Rest	EF (%)
1	1.222 ± 0.130	140 ± 30	222 ± 64	142 ± 55	32 ± 20	1.18 ± 0.16	58 ± 12
2	1.091 ± 0.024	134 ± 36	212 ± 70	169 ± 72	24 ± 13	1.22 ± 0.14	65 ± 9
*P**	†	NS	NS	NS	NS	NS	NS
3	1.015 ± 0.031	122 ± 25	173 ± 116	158 ± 91	39 ± 28	1.12 ± 0.16	62 ± 16
*P**	†	NS	NS	NS	NS	NS	NS
4	0.881 ± 0.062	116 ± 18	173 ± 50	100 ± 32	46 ± 19	0.96 ± 0.11	45 ± 13
*P**	†	0.014	0.028	0.019	NS	†	0.011

* Probability (*P*) by unpaired *t* test of group compared with group 1.
† $P < 0.001$.
BP = blood pressure; Dipyr = dipyridamole; EF = ejection fraction; Exer = exercise; FAI = percent functional aerobic impairment; HR = heart rate; Max = maximal; NS = not significant; % Δ = percent change; PRP = blood pressure × heart rate ÷ 100.

pyridamole, and in 10 of 14 (71 percent) these defects were new or increased compared with the image at rest. Thus, the diagnostic sensitivity of imaging in group 4 was comparable with that in other groups. Examination of myocardial and background count data helps explain this unexpected finding. The percent increase in myocardial counts from resting to dipyridamole images was 14.9 ± 19.3 percent for group 4 (standard error of the mean 5.2 percent), compared with 11.9 ± 22.6 percent for all patients; the percent increase in background counts was 24.7 ± 24.9 percent in group 4 (standard error of the mean 6.7 percent), compared with 2.5 ± 6.2 percent for all patients. Therefore, the absence of an increase in the M/B ratio after the administration of dipyridamole in group 4 was due primarily to greater increases in background lung activity than in other groups. Although image quality as assessed from myocardial to background ratios did not improve, myocardial thallium uptake in normally perfused areas appeared to increase normally, thus causing image defects in underperfused areas supplied by stenotic coronary arteries in the patients in group 4.

Myocardial counts/background counts after exercise compared with severity of exercise stress and left ventricular function (Table V): Patients were also ranked from the patient with the highest percent increase in M/B ratio after exercise to the patient with the highest percent decrease in this ratio compared with the values at rest and classified into four groups with an equal number of patients in each group (Table V). Changes in the M/B ratio were compared with maximal heart rate achieved during exercise, maximal pressure-rate product, functional aerobic impairment, ejection fraction and percent increase in M/B ratio after the infusion of dipyridamole. Compared with patients in the first group, patients in the fourth group had a significantly lower value for peak heart rate, maximal pressure-rate product, functional aerobic impairment and percent increase in M/B ratio with dipyridamole infusion. The second and third groups did not differ significantly from the first group in any of these measurements.

Comparison of myocardial ischemia during exercise testing and dipyridamole infusion (Table VI): Myocardial ischemia as evidenced by angina or significant S-T depression was compared for the exercise and dipyridamole studies. Angina occurred in 66 percent of all patients who underwent exercise testing and 74 percent of patients with abnormal exercise images. Angina was significantly less common and notably less severe during dipyridamole studies, occurring in 42 percent of all patients and in only 50 percent of patients with abnormal dipyridamole images. S-T depression occurred in 39 percent of all patients who underwent exercise testing and in 65 percent of patients with abnormal exercise images. S-T depression occurred in only two patients (3 percent) with dipyridamole infusion. Myocardial ischemia was less frequent during imaging with dipyridamole than during exercise stress testing, and diagnostic images were obtained in most patients without significant angina.

Effects of increased dose of dipyridamole on myocardial/background count ratio and sensitivity of thallium-201 imaging: Patients with large percent increases in myocardial/background count ratios after the administration of dipyridamole also had greater increases in supine and standing heart rates. This finding suggested that individual dose response or variation in peripheral vasodilatation and consequent heart rate response might parallel individual variation in coronary vasodilatation. Thus, an augmented dose of dipyridamole in patients with a small heart rate response to an initial standard infusion might have further increased coronary flow and the sensitivity of imaging. Accordingly, in five patients without significant left ventricular dysfunction, additional dipyridamole was administered after an initial standard infusion. After the initial standard infusion, no angina occurred, and

TABLE VI

Angina and Ischemic Electrocardiographic Changes With Exercise and Dipyridamole

	Exercise	Dipyridamole
All patients		
Angina	41 of 62 (66%)*	26 of 62 (42%)
S-T depression	24 of 62 (39%*	2 of 62 (3%)
Patients with abnormal thallium-201 image		
Angina	25 of 34 (74%)*	17 of 34 (50%)
S-T depression	22 of 34 (65%)*	2 of 34 (6%)

* Differences significant at $P \leq 0.03$ by chi square analysis.

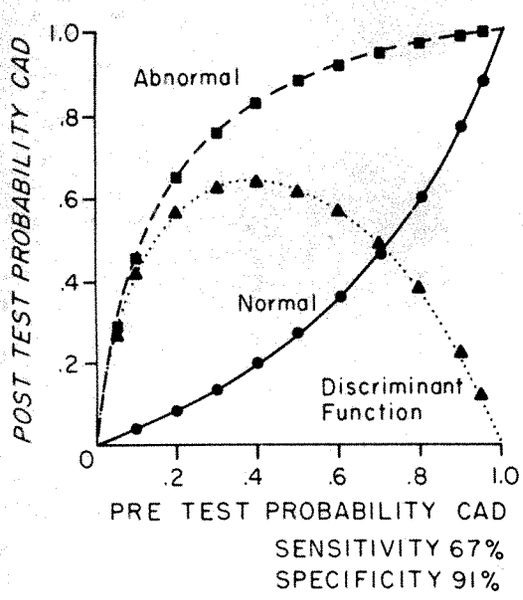


FIGURE 3. Bayes's theorem analysis of the diagnostic accuracy of a normal **(circles)** or abnormal **(squares)** thallium image after dipyridamole or exercise stress. The discriminant function **(triangles)** or difference between the normal and abnormal curves indicates the accuracy of separating normal from abnormal results. CAD = coronary artery disease.

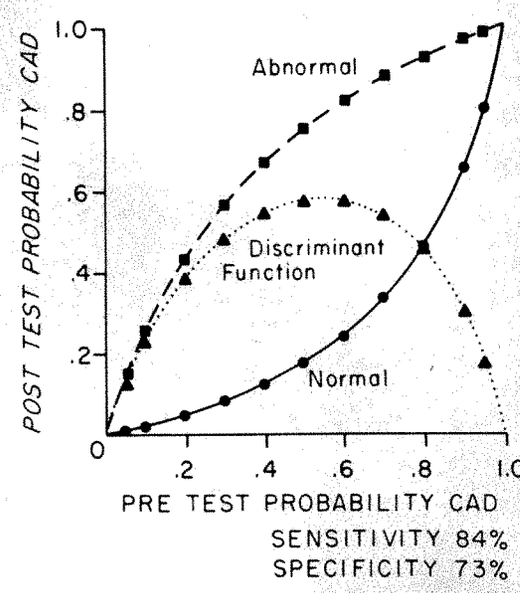


FIGURE 4. Bayes's theorem analysis of the diagnostic accuracy of a normal or abnormal result from combined electrocardiographic (ECG) and imaging study at rest and during exercise. A test was considered abnormal with any of the following: Q waves in the resting electrocardiogram, S-T depression of 1 mm or greater during exercise, or abnormal resting or exercise image, as described in Methods.

supine heart rate increased only 9 to 19 percent (mean 14 percent). A second infusion of 0.142 mg/kg per min was then administered for an additional 1.33 minutes, for a total dose of 0.76 mg/kg for the two infusions. Two minutes later the patients stood and walked in place for 1 minute, and thallium was administered. In these five patients, the standing heart rate after the administration of dipyridamole was 139 percent of the control value, compared with 138 percent for all patients receiving dipyridamole. This response suggested a comparable pharmacologic effect but at a larger dose. However, the mean myocardial/background ratio after the augmented dose of dipyridamole in the five patients was only 102 percent of the control value, compared with 112.6 percent for all patients. Image defects developed in only two of the three patients with significant coronary stenoses receiving the larger dose of dipyridamole. Although the numbers are too small to be conclusive, this finding suggests that larger dipyridamole doses may not increase sensitivity with standard thallium imaging.

Intravenous versus oral dipyridamole: Ten patients also underwent myocardial imaging after 200 mg (5 patients) or 300 mg (5 patients) of dipyridamole was administered orally as pulverized tablets in corn syrup. Supine blood pressure decreased significantly from 132 ± 16/82 ± 8 to 121 ± 17/76 ± 8 mm Hg (±1 standard deviation) 45 minutes after the oral administration of dipyridamole (P <0.03). Supine heart rate increased from 66 ± 10 to 75 ± 10 beats/min (P <0.02). Similar but greater changes in standing measurements were observed with values for blood pressure of 118 ± 18/78 ± 10 and for heart rate of 85 ± 13 at 45 minutes. Three patients had a mild headache and three mild lightheadedness after the oral administration of dipyridamole; no patient had angina or S-T segment changes in the electrocardiogram. Counts in the myocardial region increased significantly from 41.0 ± 4.5 at rest to 45.5 ± 9.3 (P <0.05), and the ratio of myocardial to background activity increased from 1.99 ± 0.27 to 2.09 ± 0.36 (P <0.05). Myocardial thallium uptake and myocardial to background activity ratios were comparable after the intravenous and oral administration of dipyridamole. Two patients who received dipyridamole orally had normal coronary arteriograms, and one had successful coronary bypass surgery between the thallium studies obtained after intravenous and oral administration of dipyridamole. The other seven patients had new or enlarged image defects after the intravenous administration of dipyridamole compared with findings in the image at rest. Six patients had new or enlarged image defects after the oral administration of dipyridamole. The diagnostic quality of the images was better after the intravenous administration of dipyridamole in three patients and after oral administration in one patient. Redistribution images were not obtained in these patients after oral or intravenous administration of dipyridamole.

Analysis of diagnostic accuracy of thallium imaging using Bayes's theorem (Fig. 3 and 4): The accuracy of applying a diagnostic test with a sensitivity of 67 percent and a specificity of 91 percent to populations with different prevalence rates of coronary disease was determined using Bayes's theorem analysis.[5-7] *Figure 3* shows, for any pre-test probability or prevalence of coronary artery disease in a group of patients, the probability of accurately categorizing an anatomically normal or abnormal patient on the basis of an abnormal or normal test result. For example, in a group of patients with a 30 to 40 percent prevalence rate of

coronary artery disease, an abnormal dipyridamole or exercise thallium image would theoretically identify the patient with disease, with an 80 percent probability of being correct. A normal image would be associated with a 15 percent probability of disease despite the normal test result. The discriminant function is the difference between the abnormal and normal curves and shows the probability of correctly separating normal from abnormal patients on the basis of the diagnostic test. For the group with a 30 to 40 percent prevalence rate of disease, exercise or dipyridamole imaging would have a 63 percent probability of correctly separating normal patients from those with coronary disease. At a lower or higher level of prevalence of disease, the ability to discriminate between normal and abnormal would decrease markedly. Trobaugh et al.[5] and Turner et al.[6,7] reported similar findings using Bayes's theorem analysis of exercise thallium imaging in patients with chest pain without prior myocardial infarction.

Figure 4 shows similar curves for combined electrocardiography and imaging at rest and during exercise. The use of either positive exercise electrocardiography or positive exercise scintigraphy as diagnostic end points increased sensitivity to 84 percent but decreased specificity to 73 percent because of the typically large number of false positive exercise electrocardiography tests. The maximal value of the discriminant function for separating normal from abnormal subjects was slightly lower for combined imaging and electrocardiographic monitoring, and the prevalence of disease at which maximal discrimination occurred was different for the two tests. Myocardial imaging alone would best separate normal from abnormal subjects in a group with a 30 to 50 percent prevalence rate of coronary disease. Combined myocardial imaging with electrocardiographic exercise testing would best separate normal from abnormal subjects in a group with a 50 to 70 percent prevalence rate of coronary disease.

Discussion

This study demonstrates that pharmacologic coronary vasodilatation with intravenous dipyridamole is as effective as maximal treadmill exercise in creating regional myocardial perfusion abnormalities detectable with thallium imaging in man.

Sensitivity and specificity of thallium imaging after exercise compared with dipyridamole infusion: The sensitivity of thallium myocardial imaging in this study is comparable with that previously reported by other investigators[6–11] but less than that reported by Botvinick et al.,[12] who defined 75 percent diameter coronary stenosis as arteriographically significant, compared with the 50 percent value used in our study. In addition, the specificity in our study was higher than in the study of Botvinick et al., indicating fewer false positive results and possibly more conservative reading of images. Infusion of dipyridamole appears particularly useful in patients who are unable to undergo maximal exercise testing. McLaughlin et al.[11] reported that the sensitivity of thallium imaging decreased with submaximal exercise stress. The usefulness of exercise imaging may therefore be limited by musculoskeletal disease, peripheral vascular disease with claudication, pulmonary disease, patient anxiety or motivation or the early onset of angina or arrhythmias. In our study, exercise testing of two patients was stopped by the physician because of hypotension; all other patients exercised to their symptom-limited maximal level. The two patients with hypotension had significant coronary disease. One had an image defect after exercise and dipyridamole; the other had no image defect with either stress and only a single 50 percent stenosis of the left anterior descending coronary artery. The latter patient's exercise hypotension may have been due to excessive doses of propranolol. Exercise testing was limited to stage I of the Bruce protocol in one patient with mild paresis of one leg. He had a 60 percent stenosis of the left anterior descending coronary artery and an anterior image defect after dipyridamole but no defect with exercise.

Myocardial ischemia with exercise versus dipyridamole: Angina occurred more frequently with exercise testing (66 percent) than with dipyridamole infusion (42 percent). Angina was considerably less severe after infusion of dipyridamole than during exercise; only two patients had significant angina, and, as in our previous study,[3] it disappeared rapidly after the intravenous administration of aminophylline, a dipyridamole antagonist. Exercise S-T depression occurred in 39 percent of all patients exercised and in 65 percent of exercised patients with image defects. S-T depression, as assessed in identical monitoring leads, occurred in only two patients (3 percent) with dipyridamole infusion. There are several possible explanations for myocardial ischemia during dipyridamole infusion.[3] A mild increase in myocardial oxygen consumption has been described after the intravenous administration of dipyridamole, possibly as a consequence of increased heart rate or increased coronary flow. "Coronary steal" with an absolute decrease in regional myocardial or subendocardial perfusion might also occur. Unfortunately, external thallium imaging cannot be used to quantitate coronary flow and identifies only relative differences in myocardial perfusion. Therefore, we cannot determine the relative importance of increased myocardial oxygen demands or an absolute decrease in myocardial oxygen supply as the cause of angina in our patients. Because no angina or S-T changes occurred in 50 percent of patients with image defects after the administration of dipyridamole, we surmise that dipyridamole most commonly produced relative perfusion abnormalities without overt ischemia.

Mechanism, safety and optimal dose of dipyridamole infusion: Dipyridamole may induce coronary vasodilatation by several mechanisms. Adenosine, a product of adenine nucleotide utilization in myocardial tissue, has vasodilator activity and has been proposed as a coronary vasoregulator. Dipyridamole prevents inactivation of adenosine by adenosine deaminase in the red blood cells and lung and myocardial tissues, either by inhibiting adenosine deaminase or by preventing the uptake of adenosine into these tissues.[13] Dipyridamole also has a direct effect of sensitizing coronary vascular

tissue to the vasodilating effects of a given concentration of adenosine.[14]

Dipyridamole (0.142 mg/kg per min for 4 minutes) was administered safely to 62 patients in this study, including 51 patients with significant coronary artery disease as assessed with angiography. In 5 of the 24 patients with previous myocardial infarction, ejection fraction was less than 30 percent. Patients with left ventricular dysfunction or severe coronary disease but stable angina experienced no untoward effects. Any subject with angina at rest was excluded from both dipyridamole and exercise testing. No patient experienced hypotension after receiving the standard infusion and walking in place immediately after standing. We previously reported[3] on one patient who had significant orthostatic hypotension with a decrease in blood pressure from 120/75 mm Hg supine to 80/40 mm Hg standing after receiving an intravenous bolus injection of 0.57 mg/kg of diypridamole. Supine blood pressure was normal. This patient also had symptomatic hypotension after sublingual administration of isosorbide dinitrate and in two separate instances during recovery from exercise (while not receiving drugs), although he did not have hypotension during exercise.

Diagnostic sensitivity of thallium imaging was unrelated to myocardial/background (M/B) ratios of either exercise or dipyridamole images. Incomplete data suggested that augmented doses of dipyridamole over the standard infusion did not increase either M/B ratios or diagnostic sensitivity. Oral dipyridamole produced definite pharmacologic effects with mild but statistically significant decreases in blood pressure, increases in heart rate and increases in myocardial uptake of thallium in 10 patients. Further studies are necessary to determine the safety, optimal drug dose and diagnostic sensitivity of imaging after oral dipyridamole.

Comparison of myocardial imaging after dipyridamole and exercise: Intravenous dipyridamole has been shown to increase coronary flow maximally in chronically instrumented dogs and to increase coronary flow fourfold in man. Reported responses of coronary flow during exercise in man vary widely depending on the method used to measure coronary flow. It is therefore difficult to determine whether exercise in man is comparable with dipyridamole as a stimulus for coronary flow. Myocardial to background ratios for dipyridamole images were higher than for exercise images in this study, suggesting that dipyridamole caused a larger increase in relative coronary blood flow in these patients. However, sensitivity and specificity in identifying significant coronary stenoses were identical for dipyridamole and exercise images.

As determined with external imaging, the myocardial uptake of thallium during exercise was lower than the uptake of thallium injected at rest. In contrast, the myocardial uptake of thallium injected after dipyridamole was higher than the uptake of thallium injected at rest. One possible explanation for these changes, in oversimplified terms, would be as follows: Total myocardial uptake of a systemically administered radionuclide is determined by the fraction of cardiac output going to the myocardium.[15] According to the Fick principle, cardiac output equals the total injected dose of radionuclide divided by the integrated arterial time-concentration curve; myocardial uptake equals the integrated arterial time-concentration curve times coronary blood flow times the percent extracted. Consequently, myocardial uptake depends on the ratio between coronary blood flow and cardiac output for a fixed injected dose of radionuclide: $U_M = (CBF/CO)(D)(E)$, where U_M is the myocardial uptake of the radionuclide, CO is cardiac output in ml/min, CBF is coronary blood flow in ml/min, D is the injected dose in mCi and E is the percent extracted. If coronary blood flow doubled and cardiac output remained the same, the myocardial uptake of the radionuclide would double if extraction were constant. If coronary blood flow and cardiac output both doubled, then the fractional cardiac output going to the myocardium and radionuclide uptake would remain the same, again if extraction were constant. This equation may therefore explain the decrease in myocardial thallium activity with exercise. If cardiac output increased more than coronary blood flow during exercise, the fraction of cardiac output going to the myocardium would decrease, and the absolute counts in myocardium would also decrease despite an increase in absolute coronary blood flow. After infusion of dipyridamole, if coronary flow increased more than cardiac output, myocardial uptake of thallium would increase.

Changes in thallium extraction at different coronary flow rates or metabolic conditions, as in exercise, are complicating problems. Bull et al.[16] reported data that directly support this explanation. With bicycle exercise, thigh muscle uptake of thallium increased much more than myocardial uptake of thallium, and with dipyridamole the opposite occurred. They also found that pulmonary uptake of thallium decreased with exercise and increased with dipyridamole, as we observed. Strauss et al.[17] utilized whole body thallium imaging to visualize regional cardiac output in experimental animals and man. The concept underlying their approach is the same as that we have proposed to explain our results. Some reported data in man[18,19] indicate that, during exercise, cardiac output may increase more than coronary blood flow, or at least as much.[20] Other data suggest that cardiac output may increase less than coronary blood flow during exercise.[21,22]

For stress images of adequate overall quality for clinical interpretation, the degree of myocardial thallium uptake or myocardial/background ratios did not parallel diagnostic sensitivity. The reason is that sensitivity of stress imaging is a function of the increase in *absolute* coronary blood flow,[2] whereas myocardial uptake and myocardial to background activity ratios are a function of the fractional cardiac output going to the myocardium.

There are distinct advantages and disadvantages of dipyridamole imaging compared with exercise imaging. The major advantages are that dipyridamole imaging can be performed easily and in patients who are unable or unwilling to undergo maximal treadmill stress. The major disadvantage is the absence of additional diagnostic information provided by the S-T segment re-

sponse during exercise. The sensitivity of identifying coronary artery disease with combined electrocardiographic and imaging abnormalities at rest or on exercise is greater than with exercise or dipyridamole imaging alone. However, this increase in sensitivity is offset by a decrease in specificity due to the large proportion of false positive results with electrocardiographic exercise testing. The addition of electrocardiographic criteria to imaging at rest and on exercise does not increase the maximal value of the discriminant function, that is, the overall accuracy of separating normal from abnormal patients. However, it does shift the peak of the discriminant function from a lower to a higher prevalence rate. The consequence of this shift is to make combined electrocardiographic imaging techniques less accurate and imaging alone more accurate for separating normal from abnormal responses in groups that have a lesser prevalence of disease, such as asymptomatic persons. In groups of patients with a prevalence rate of disease that is probably higher than 40 percent, such as patients with chest pain syndromes, a combined electrocardiographic imaging technique would be more accurate than imaging alone for separating normal from abnormal responses. Thus, the utility of combined electrocardiographic imaging techniques versus imaging alone depends on the population being tested.

Clinical application: The relative advantages or disadvantages of pharmacologic coronary vasodilators versus exercise cannot be fully evaluated at present because of inherent limitations of the imaging process itself or limitations inherent in the imaging agent, or both. Although many technical factors such as redistribution and resolution may contribute to less than optimal diagnostic sensitivity and specificity, experimental evidence suggests that two other basic problems remain the major limiting factors in diagnostic myocardial imaging. The first problem is inherent in the radionuclide thallium-201, whose uptake in myocardium is not directly proportional to flow at high coronary flow rates, as discussed previously.[2,23] The second problem is due to overlying myocardial structures and lung that may obscure areas of mildly decreased relative perfusion. Within these recognized limitations, this study has defined the usefulness of myocardial perfusion imaging with pharmacologic coronary vasodilators using current, readily available technology. Further advances in imaging agents or cross-sectional myocardial tomography, or both, will be necessary before imaging techniques become satisfactory for the noninvasive, reliable diagnosis of coronary disease, particularly in asymptomatic persons.

Acknowledgment

We acknowledge the outstanding technical work of Ann Coleman and Mike Robertson in this study.

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In Liquid Potassium Therapy

A GREAT NEW WAY TO START THE DAY

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Each effervescent tablet in solution supplies 50 mEq potassium as bicarbonate and citrate.

And in good-tasting orange and lime flavors

- Easy dosage to remember in preferred liquid form—50 mEq potassium/tablet.
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- A record of safety...no reports of GI ulceration in over a decade of use of original K-LYTE®*
- Cost is less than a diet of potassium-rich foods.

*See Prescribing Considerations

Prescribing Considerations

Indications: K-LYTE DS, is an oral potassium supplement for therapy or prophylaxis of potassium deficiency. It is particularly useful when thiazide diuretics, corticosteroids, or severe vomiting and diarrhea cause excessive excretory potassium losses; and when dietary potassium is low. Carefully monitored, K-LYTE DS may also be useful for potassium replacement where digitalis intoxication results in cardiac arrhythmias.

Contraindications: Impaired renal function with oliguria or azotemia; Addison's disease; hyperkalemia from any cause.

Warnings and Precautions: Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients and such patients should be monitored by ECG for cardiac irregularities. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, **patients should be carefully directed to dissolve each dose completely in the stated amount of water.**

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

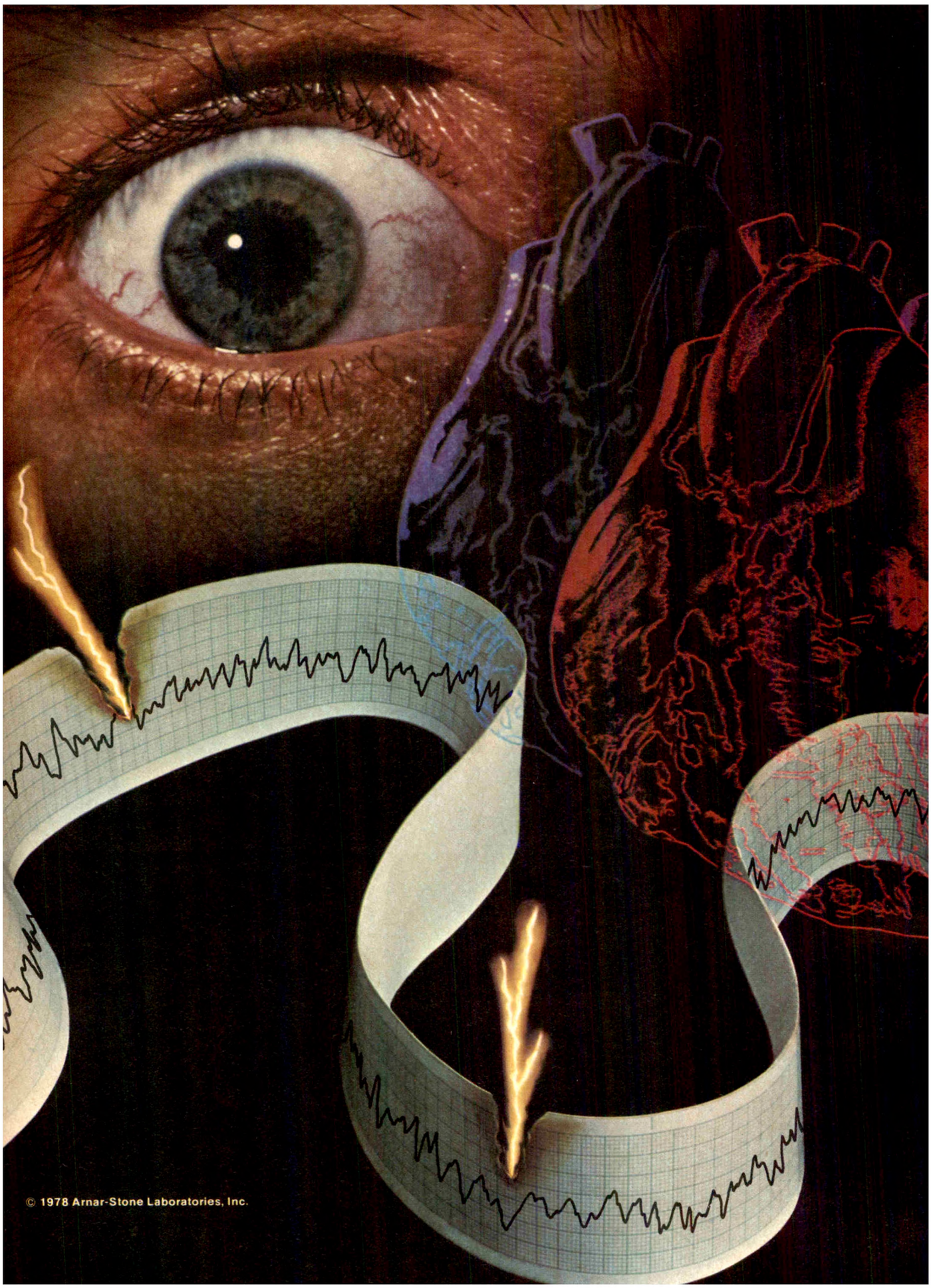
Dosage and Administration: Adults: 1 tablet completely dissolved, 1 to 2 times daily, depending upon the requirements of the patient: 1 tablet (50 mEq. potassium) in 6 to 8 ounces of cold or ice water. The normal adult daily requirement is approximately 50 mEq. of elemental potassium.

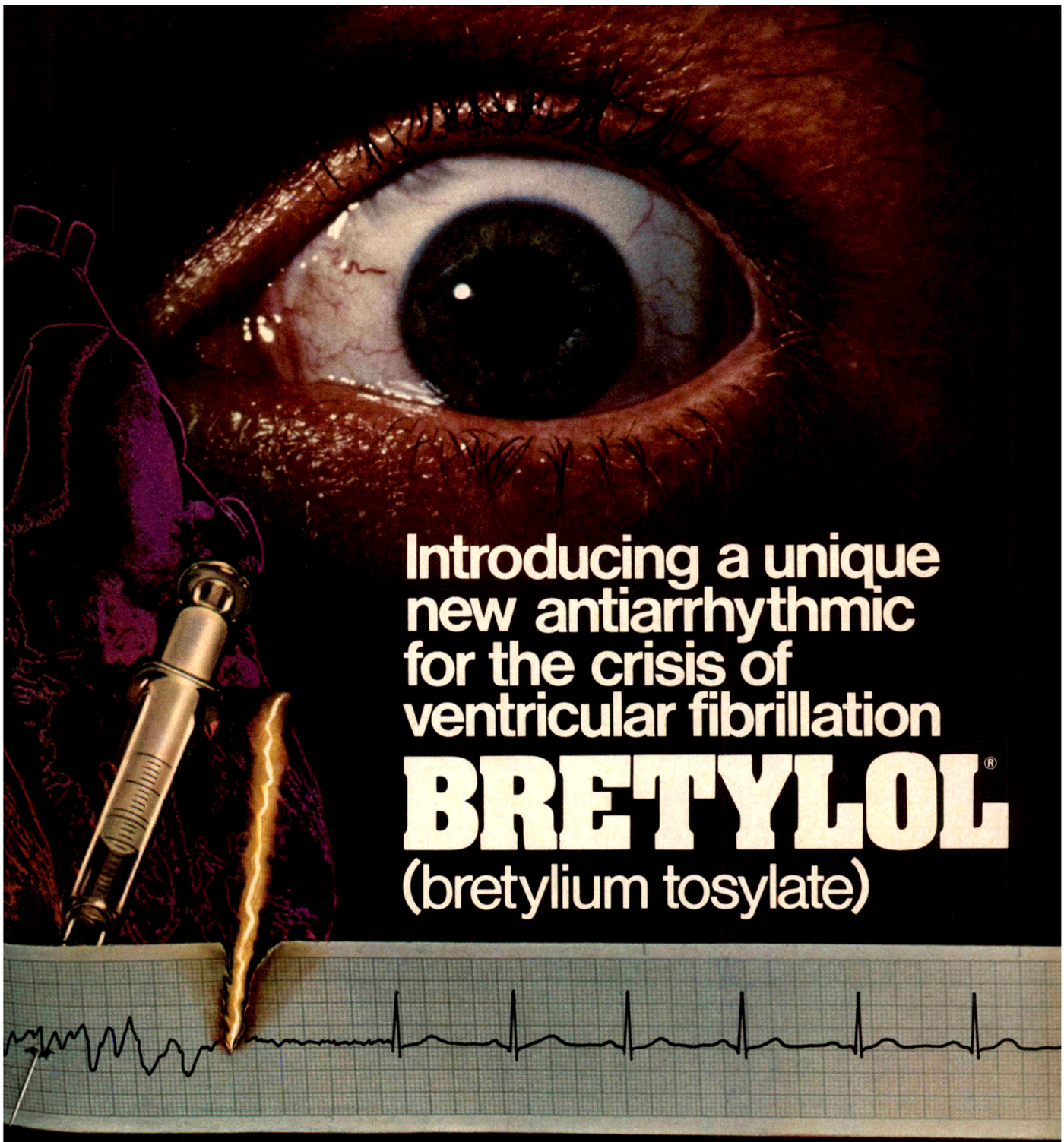
NOTE: It is suggested that K-LYTE DS be taken with meals and sipped slowly over a 5-10 minute period.

How Supplied: K-LYTE DS effervescent tablets (orange or lime flavors) are available in cartons of 30 individually foil-wrapped tablets. **Also available,** K-LYTE (25 mEq. potassium) effervescent tablets (orange or lime flavors) in cartons of 30 and 250.

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Introducing a unique new antiarrhythmic for the crisis of ventricular fibrillation

BRETYLOL®

(bretylium tosylate)

Not meant to imply time relationship between administration of Bretylol and patient response.

BRETYLOL® (bretylium tosylate) is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to first-line therapy.

At present, Bretylol should not be considered a first-line antiarrhythmic agent. Use of Bretylol should be limited to facilities where equipment for constant monitoring of arrhythmias is available.

BRETYLOL® bretylium tosylate

BRETYLOL: in ventricular fibrillation

In reported clinical situations, BRETYLOL® (bretylium tosylate) was effective in conjunction with electrical cardioversion, even in patients refractory to other antiarrhythmic therapies. BRETYLOL raised the ventricular fibrillation threshold in animal studies. Suppression of ventricular fibrillation usually occurs within minutes following intravenous administration, the effect generally lasting 6 to 8 hours.

BRETYLOL: in ventricular tachycardia

In clinical studies, BRETYLOL was effective in the management of ventricular tachycardia and other ventricular ectopic rhythms, even those recurrent and refractory to existing antiarrhythmic therapies. Clinical benefits can usually be observed 20 minutes or more following parenteral administration with duration of action 6 to 8 hours.

BRETYLOL: effects on cardiac function

Unlike other antiarrhythmic drugs, BRETYLOL has demonstrated (in animal studies) a positive inotropic effect on the myocardium and did not significantly decrease A-V conductivity. In man, BRETYLOL generally did not depress myocardial function and maintained cardiac output. These effects may be due to release of norepinephrine from nerve terminals, potentiation of the effects of endogenous catecholamines and/or a direct action on the myocardium.

BRETYLOL: contraindications/adverse reactions

There are no contraindications for BRETYLOL in the treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

The principal adverse reaction is hypotension, usually postural. This is due to reduction of peripheral vascular sympathetic tone, *not* to depression of myocardial function.

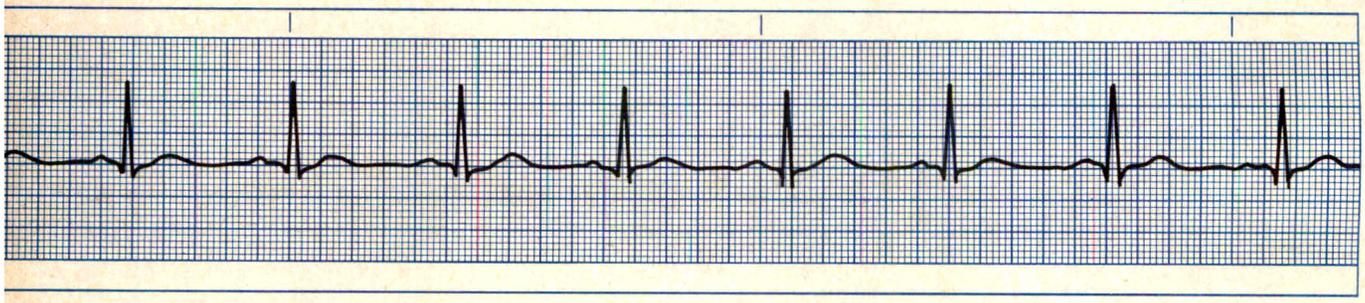
Due to the initial release of norepinephrine from the adrenergic postganglionic terminals, there may be initial *transient* increases in blood pressure, heart rate and/or PVC's. These generally return promptly to preadministration levels.

Nausea and vomiting can usually be obviated by the slow intravenous administration of a dilute solution of BRETYLOL.

For a full description of adverse reactions, please refer to the complete prescribing information on the last page of this advertisement.

ARNAR-STONE LABORATORIES, INC.

McGaw Park, Illinois 60085
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BRETYLOL® bretylium tosylate

BRETYLOL® (bretylium tosylate) Bibliography

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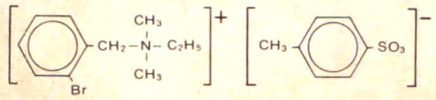
BRETYLOL® bretylium tosylate

BRETYLOL INJECTION

FOR INTRAMUSCULAR OR INTRAVENOUS USE

DESCRIPTION

BRETYLOL (bretylium tosylate) is o-Bromobenzyl ethyldimethylammonium p-toluene sulfonate. The chemical structure is:



$C_{18}H_{24}BrNO_3S$ Mol. Wt. 414.39

BRETYLOL is a white, crystalline powder with an extremely bitter taste. It is freely soluble in water and alcohol. Each ml of sterile, pyrogen-free solution contains 50 mg bretylium tosylate in Water for Injection, USP. The pH is adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. BRETYLOL contains no preservative.

CLINICAL PHARMACOLOGY

BRETYLOL (bretylium tosylate) is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

BRETYLOL also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibillation threshold.

2. Increase in action potential duration and effective refractory period without changes in heart rate.

3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.

4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by BRETYLOL, but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because BRETYLOL causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, BRETYLOL blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of BRETYLOL and peak hypotensive effects were seen within one hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6-9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. No metabolites have been identified following administration of BRETYLOL in man and laboratory animals. In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose is excreted in the urine during the first 24 hours, with an additional 10% excreted over the next three days.

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. Since there is a delay in onset of its antiarrhythmic action, BRETYLOL is not to be considered or used as a replacement for rapidly-acting antiarrhythmic agents currently in use. The clinical use of BRETYLOL is for short-term use only. Patients should either be kept supine during the course of BRETYLOL therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of BRETYLOL has not been determined. There is comparatively little experience with dosages greater than 30 mg/kg/day, although such doses have been used without apparent adverse effects. The following schedule is suggested:

A. For Immediately Life-threatening Ventricular Arrhythmia, as in Ventricular Fibrillation: Administer undiluted BRETYLOL at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated at 15 to 30 minute intervals until a total dose of not more than 30 mg/kg of body weight has been given. For maintenance dosage, see below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as follows before intravenous administration:* Using aseptic technique, dilute contents of one BRETYLOL ampul (10 ml containing 500 mg bretylium tosylate) to a minimum of 50 ml with Dextrose Injection, USP or Sodium Chloride Injection, USP.

Administer the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg of body weight by intravenous infusion over a period greater than 8 minutes. More rapid infusion may cause nausea and vomiting. A second dose may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: (*Do not dilute BRETYLOL prior to intramuscular injection.*) Inject 5 to 10 mg BRETYLOL per kg of body weight. Dosage may be repeated in 1 to 2 hours if the arrhythmia persists. Thereafter maintain with same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and the site of injection should be varied on repeated injection.

C. Maintenance Dosage: The diluted BRETYLOL solution may be administered by intermittent bolus infusion or by constant infusion.

1. Intermittent Infusion: Infuse the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion may cause nausea and vomiting.

2. Constant Infusion: Infuse the diluted solution at a dosage of 1 to 2 mg BRETYLOL per minute.

Dosage of BRETYLOL should be reduced and discontinued in 3 to 5 days under electrocardiographic monitoring. Other appropriate antiarrhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP, pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, pyrogen-free. July 1978

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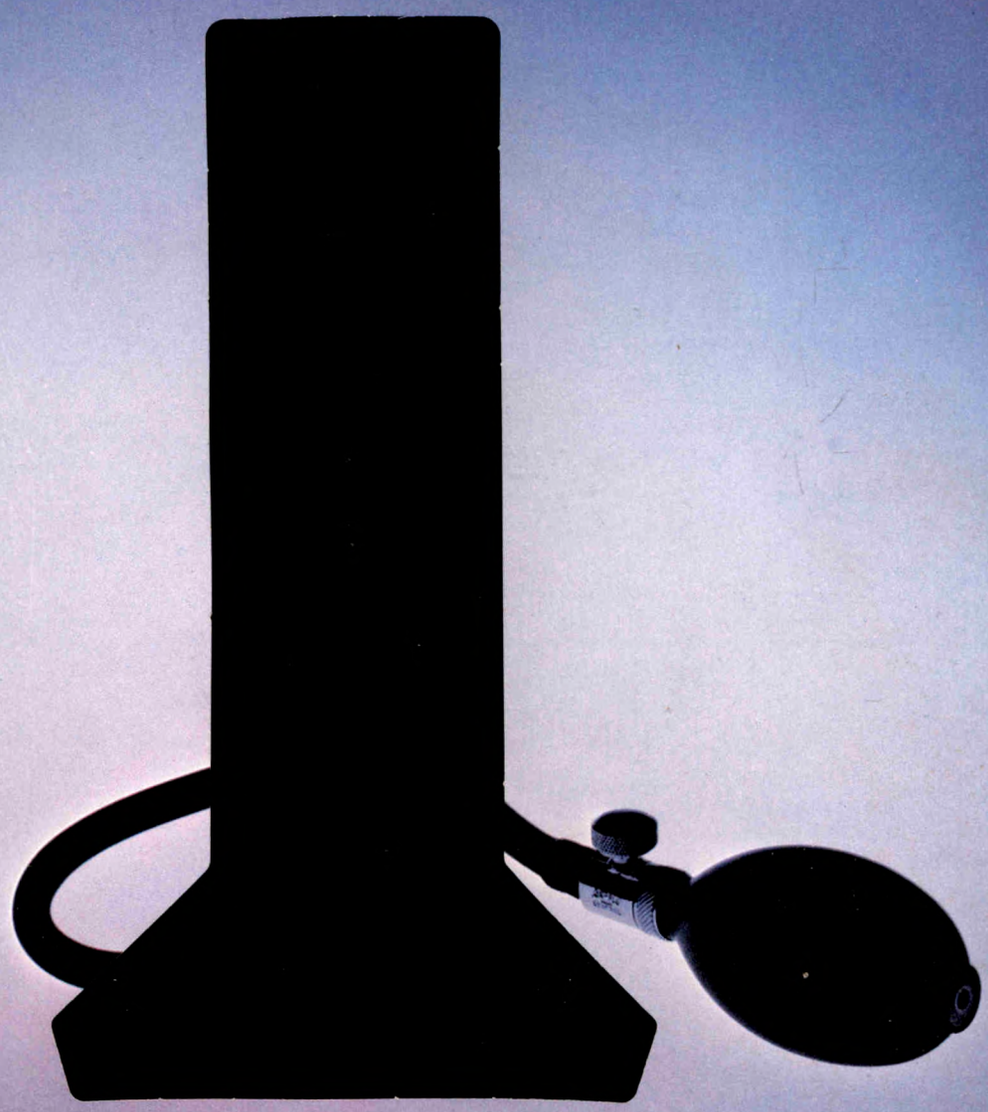
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HYPERTENSION DEMANDS MORE THAN JUST EFFECTIVE CONTROL...



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YEARS OF BLOOD PRESSURE CONTROL

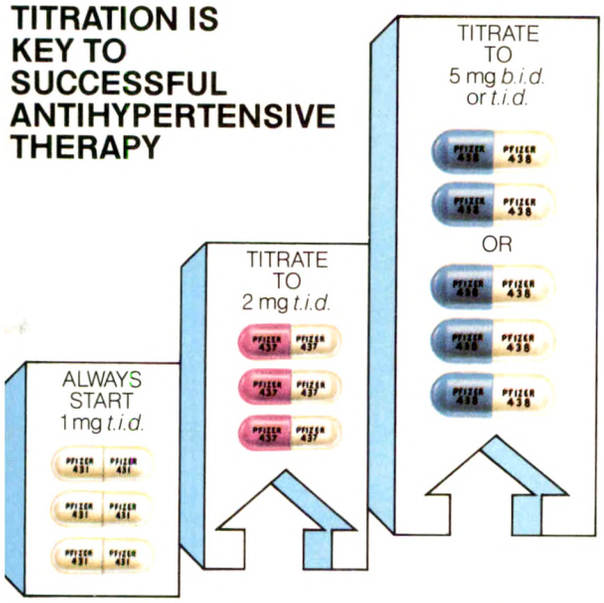
- Effectively controls blood pressure over the long term* without compromi cardiac or renal function. Reflex tachycardia frequently associated with c vasodilators is much less common with Minipress.
- Effective Step 2 antihypertensive agent when combined with a diuretic.
- Effectiveness enhanced when combined with a diuretic and/or other anti-hypertensive agents.
- Limited potential for organ toxicity. Laboratory abnormalities such as positive Coombs' tests have not been a problem with Minipress therapy.
- Few persistent side effects. The most common reactions have generally been mild


WITHOUT COMPROMISE OF VITAL ORGANS
Please see Brief Summary on last page
Before prescribing Minipress, WARNINGS
and DOSAGE AND ADMINISTRATION
MINIPRESS® Capsules 1mg, 2mg, 5m
prazosin HC

EARS OF BLOOD PRESSURE CONTROL...WITHOUT COMPROMISE OF VITAL ORGANS

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

TITRATION IS KEY TO SUCCESSFUL ANTIHYPERTENSIVE THERAPY



USUAL MAXIMUM DAILY DOSAGE: 20 mg given in divided doses *(b.i.d.* or *t.i.d.)*. A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

Initial therapy: Whether using Minipress in ombination with other agents or alone, the start- g dosage is 1 mg *t.i.d.* If response is not adequate the next visit, the dosage should be increased 2 mg *t.i.d.*

Dosage titration: Thereafter, titrations of inipress should be carried out according to atient response. Dosage may be slowly increased a daily maximum of 20 mg given in divided oses. Although some patients may be controlled 1 mg *t.i.d.*, generally 6 mg to 15 mg daily will e needed in the majority of responding patients order to achieve optimal blood pressure control.

Maintenance therapy: After initial titration, atients may be maintained on a *b.i.d.* or *t.i.d.* osage regimen.

If optimum control is not achieved in patients ceiving Minipress and a diuretic, consider adding nother Step 2 antihypertensive agent.

If optimum control is not achieved with Minipress the initial agent, consider adding a diuretic.

When adding a diuretic or other antihyperten- ve agent, Minipress dosage should be reduced 1 mg or 2 mg *t.i.d.* and retitrated as needed.

Available in 1-mg, 2-mg, and 5-mg capsules.

REMOVE PAGE AND FOLD ALONG DOTTED LINE AND SAVE FOR REFERENCE

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug;occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

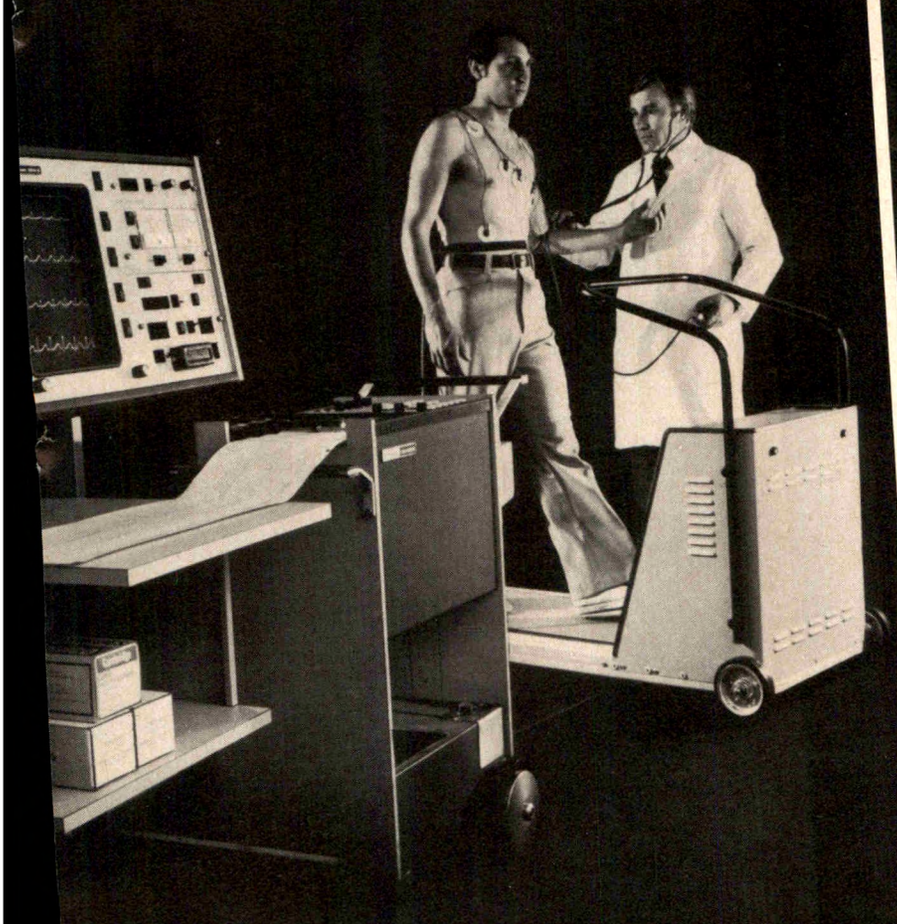
Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit-dose institutional packages of 100 (10 x 10's).

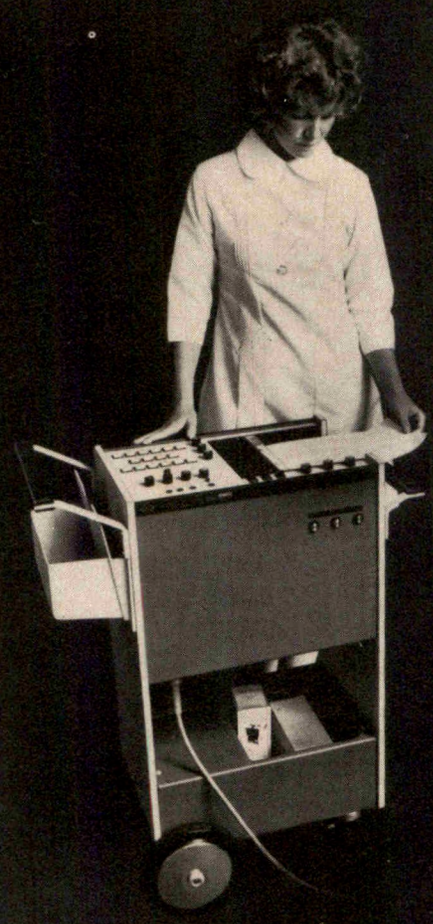
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11:49 A.M. It's a Stand-alone Electrocardiograph



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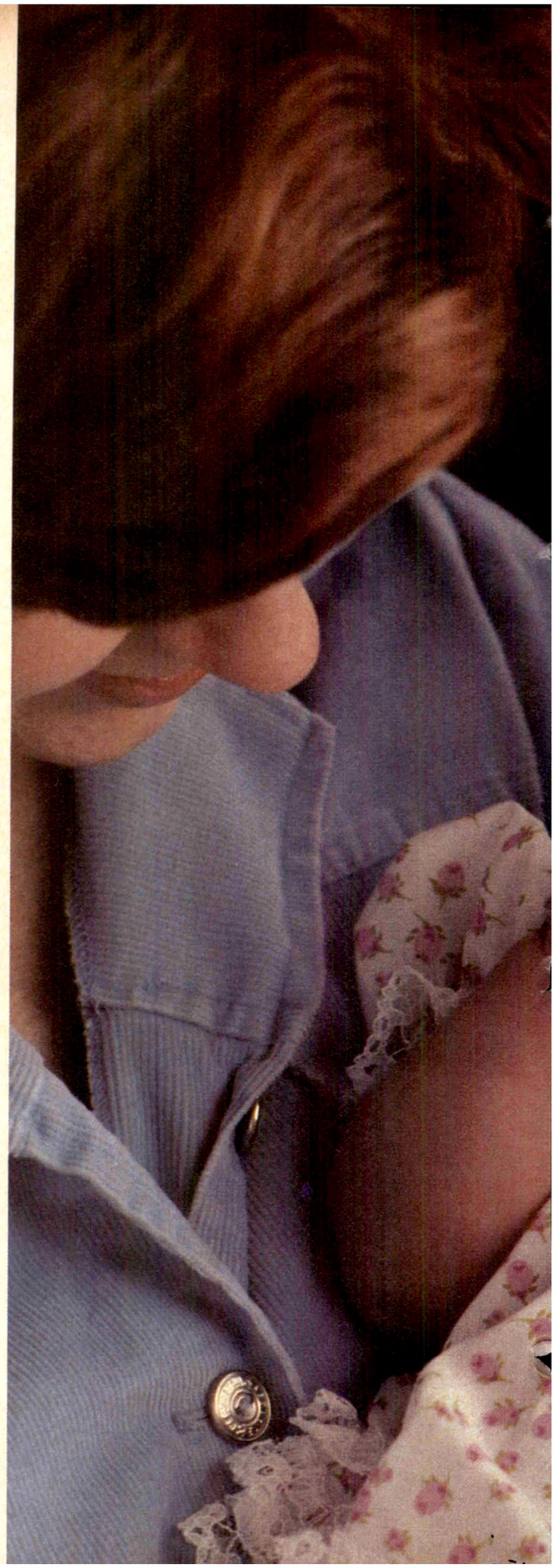
Warranty statement available upon request

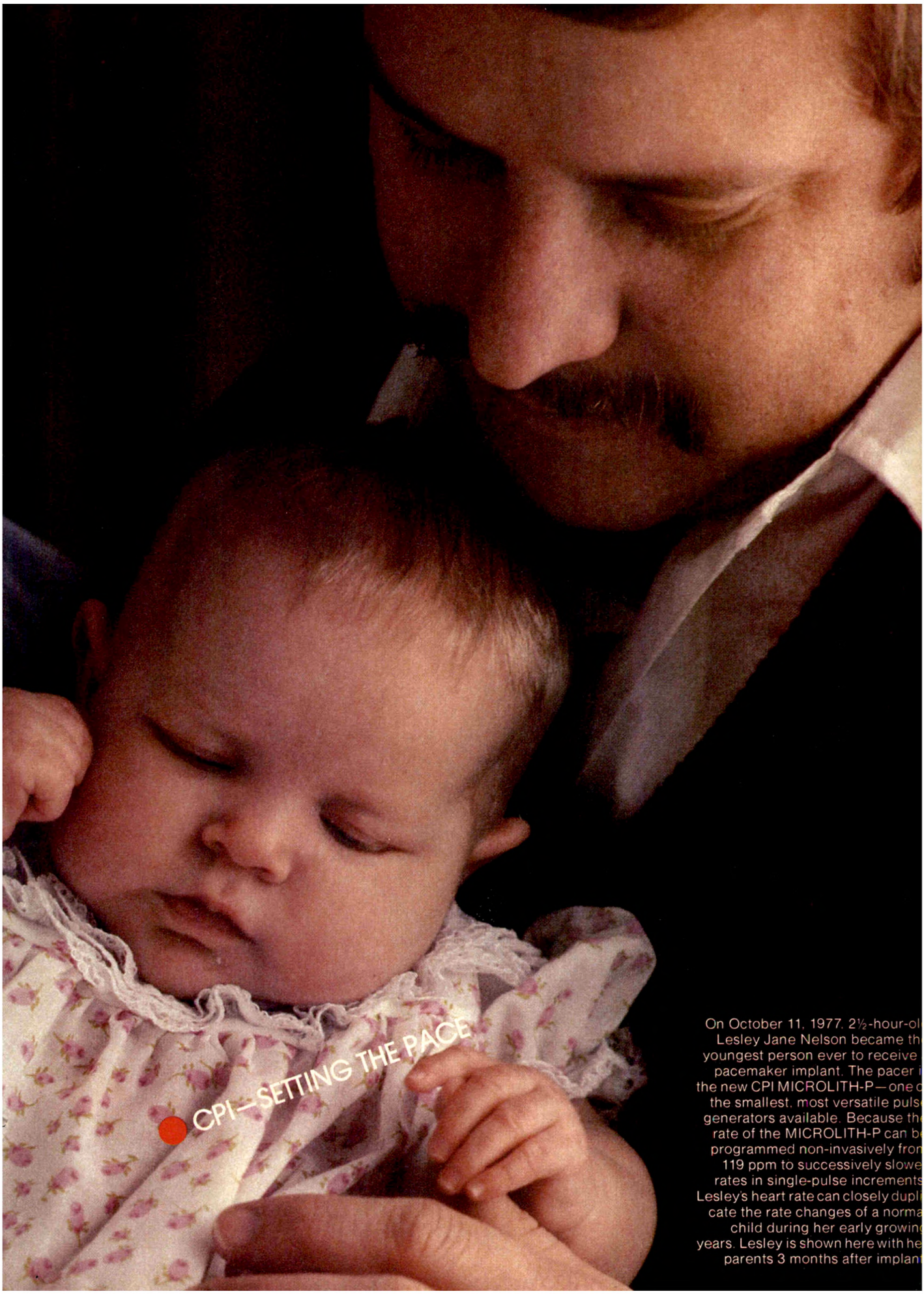


CPI®

Cardiac Pacemakers, Inc.
4100 North Hamline Avenue
P.O. Box 43079
St. Paul, Minnesota 55164, U.S.A.
Telephone: (612) 631-3000
Cable: Cardiapace, St. Paul
Telex: 29-7049

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On October 11, 1977, 2½-hour-ol
Lesley Jane Nelson became th
youngest person ever to receive
pacemaker implant. The pacer i
the new CPI MICROLITH-P—one o
the smallest, most versatile puls
generators available. Because th
rate of the MICROLITH-P can b
programmed non-invasively fro
119 ppm to successively slowe
rates in single-pulse increments
Lesley's heart rate can closely dupli
cate the rate changes of a norma
child during her early growin
years. Lesley is shown here with he
parents 3 months after implan


Dyna-Mite T.M.
MODEL 5200
SERIAL NO.
POWER
OFF
ON
RECORD
CAL
ECG
GAIN
1/2
1
MINUTES
Dyna-Gram ®
PATIENT'S NAME
DATE
MODEL 5085
24
HOURS

Introducing the new lightweight champion

Cardio-Dynamics new Holter recorder weighs in at a trim 10 ounces of rugged physical perfection

It's a unanimous decision.

Dyna-Mite—our new, Model 5200, three-channel, 24-hour ECG recorder—is a technical knockout!

At a mere 10 ounces, it's the lightest Holter recorder available. Add the battery and tape cassette and it's still the lightweight champ. And, that wins comfort for your patients.

Three channels and plenty of range.

Light and trim as it is, Dyna-Mite doesn't give up a thing in power and performance. Ten years of Holter experience stands behind its design and capability. Three channels simultaneously record an independent timing track plus two ECG leads (modified V_1 and V_5), for optimum assistance in verifying the ventricular or supraventricular origin of ectopic beats.

Recording clarity and accuracy is further assured by Dyna-Mite's, American Heart Association approved, frequency response range of .05-100 Hz. Move the Gain switch to the ½-position and you virtually double the dynamic recording range without ECG signal distortion. Calibration is a snap with Dyna-Mite's internal system.

Patient motion artifacts, electrode offset potentials, baseline wander and other extraneous signals are remarkably compensated for by Dyna-Mite's precision, high-input impedance, amplifier circuitry.

A combination of style and performance. Guaranteed to go the 24-hour distance.

Worn on a belt or in a soft leatherette pouch, Dyna-Mite is almost inconspicuous. It is guaranteed to provide a full 24 hours of unvaried recording when powered by Cardio-Dynamics own, economic, disposable battery. A convenient, patient-activated, event button provides for timing track marking precisely when symptoms are experienced. A digital clock clearly displays the time for easy, patient diary notation. Thus, identification of every event and its correlation with the ECG and patient activity is aided during analysis.

To assure you of consistent high quality ECG recording, Cardio-Dynamics also manufactures Dyna-Mite, 24-hour, recording cassettes. Every cassette is examined for magnetic linearity, internal friction, signal-to-noise ratio, and mechanical stretching and stacking before it receives the Cardio-Dynamics name.

Designed for years of rugged use, every Dyna-Mite recorder is warranteed for one full year. Thereafter, Cardio-Dynamics provides ongoing service and has economic service policies available.

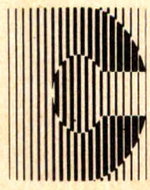
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the most comprehensive company in Holter recording

Dyna-Mite recorder shown ⅞ actual size.



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Los Angeles, California 90064

☐ Please send me more information about Dyna-Mite and your Holter supplies and services.

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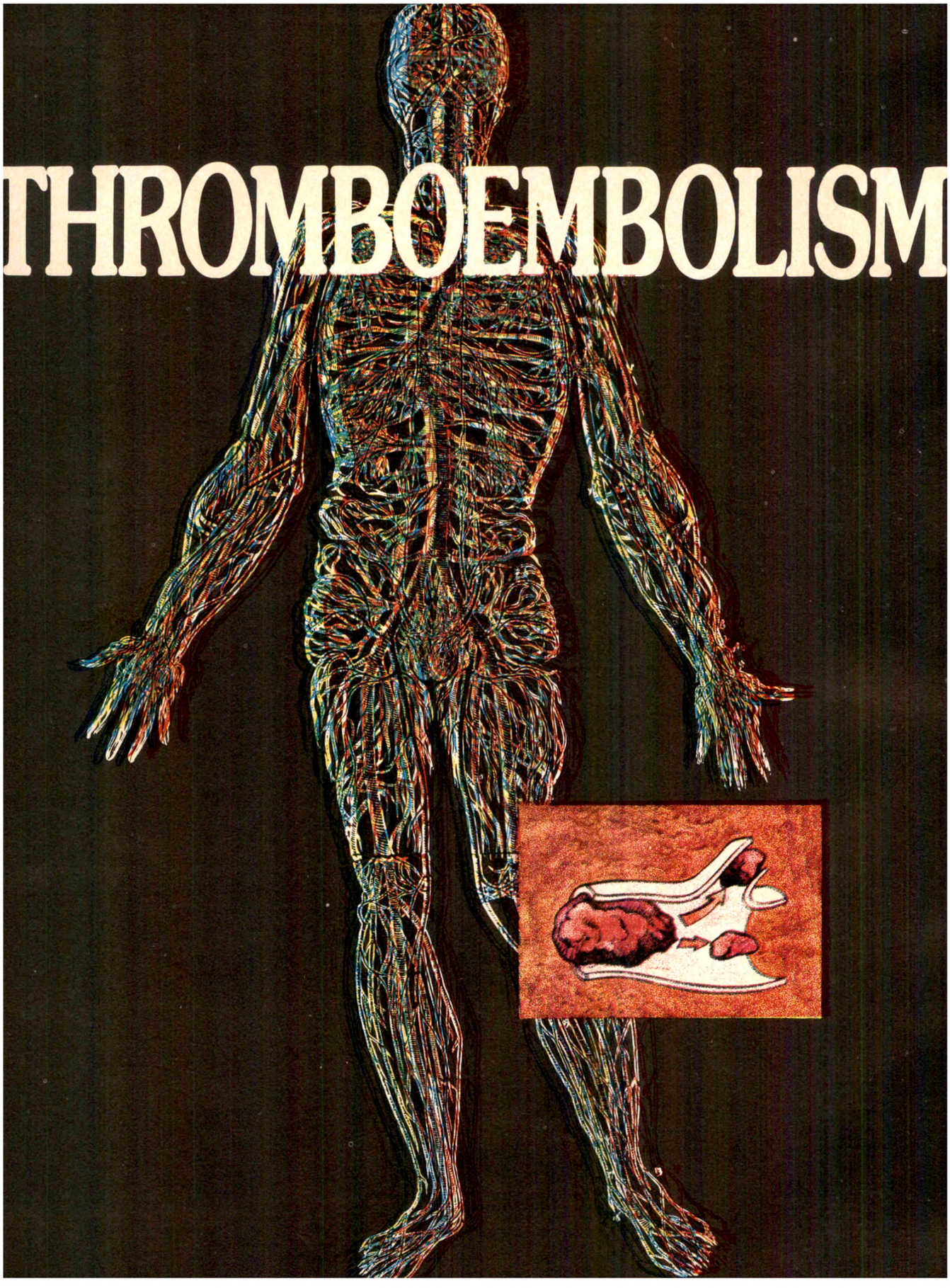
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THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion**, eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN* are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN*, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN* overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN* with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN* may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN*, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN* may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN* administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

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6037-10

EDO-046C

March, 1977

Assessment of Coronary Stenoses With Myocardial Perfusion Imaging During Pharmacologic Coronary Vasodilatation

IV. Limits of Detection of Stenosis With Idealized Experimental Cross-Sectional Myocardial Imaging

K. LANCE GOULD, MD, FACC

Seattle, Washington

Because atherosclerosis may be reversible, a routine noninvasive screening test for the reliable diagnosis of mild coronary arterial lesions would allow potential prevention of coronary events in specific patients through intensive dietary management, drug therapy and physical training. To determine the minimal coronary stenosis detectable with myocardial perfusion imaging techniques, standardized stenoses ranging from 31.4 to 72.5 percent diameter narrowing were applied to the left circumflex coronary artery of 12 open chest dogs. Indium-113m–labeled human albumin microspheres were injected into the left atrium under control conditions and technetium-99m human albumin microspheres during maximal coronary vasodilatation induced with intravenous dipyridamole. Hearts were removed, sliced into 1 cm thick cross sections and imaged under a gamma camera. The results demonstrate that 40 percent diameter coronary stenoses can be identified by imaging relative subendocardial underperfusion during pharmacologic coronary vasodilatation. An imaging technique sensitive enough to identify mild coronary lesions for diagnostic screening purposes requires (1) a potent stimulus for coronary vasodilatation, such as intravenous dipyridamole; (2) an imaging agent taken up by the myocardium in proportion to coronary flow at flow rates up to four or more times resting coronary flow so that differences in regional maximal flows caused by mild stenoses can be identified; and (3) cross-sectional tomographic myocardial imaging to visualize relative endocardial-epicardial perfusion, the most sensitive indicator of the hemodynamic effects of coronary stenoses, and to exclude from the imaging field the interfering activity of lung, background and overlying heart structures.

Unexpected sudden death, myocardial infarction or new angina pectoris usually indicates advanced coronary artery disease in which severe narrowing of one or more coronary arteries has been present for some time before becoming clinically manifest. Because atherosclerosis may be reversible,[1,2] a routine noninvasive screening test for the reliable diagnosis of mild coronary lesions would permit potential prevention of these sequelae in specific patients through intensive dietary management, drug therapy and physical training. The regression or progression of the lesions could be followed up by repeated tests. The most useful noninvasive test now currently available for detecting and localizing myocardial ischemia in patients with symptoms of coronary disease utilizes myocardial imaging of thallium-201 injected at rest and during maximal treadmill exercise.[3–11] Although thallium-201 myocardial imaging has been an important development in the noninvasive diagnosis of coronary disease, it gives false negative results in 19 to 39 percent[3–11] of patients with arteriographically significant coronary lesions. The false

From the Veterans Administration Hospital and the Department of Medicine, University of Washington, Seattle, Washington. This study was supported by the Veterans Administration Medical Research Service, Seattle, Washington; Grant 63-2749 from the Washington Heart Association, Seattle, Washington; and by Grant HL 18492 from the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland. Manuscript received March 21, 1978; revised manuscript received June 20, 1978, accepted June 28, 1978.

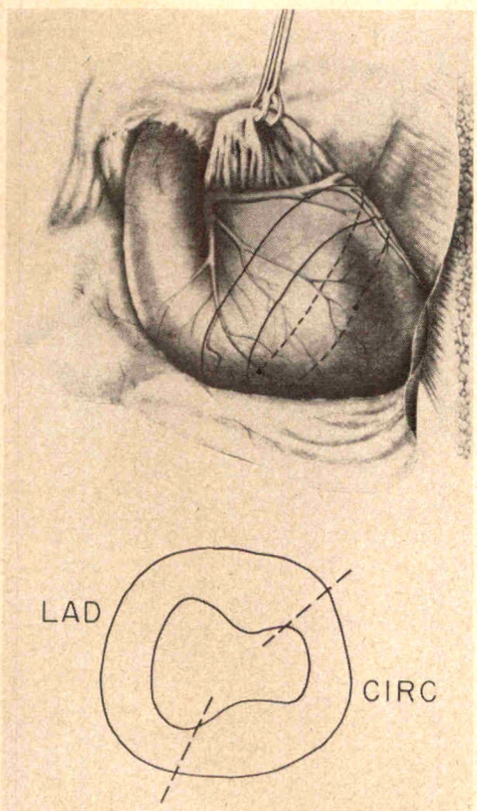
Address for reprints: K. Lance Gould, MD, Veterans Administration Hospital, 4435 Beacon Avenue South, Seattle, Washington 98108.

egative results are highly dependent on the specific oronary arteries affected and on the presence of one, wo or three vessel involvement.[11] Thallium imaging is herefore of limited value as a screening procedure, articularly when applied to an asymptomatic popu- ation in which the prevalence of disease is less than 15 ercent.[12–14]

Among the reasons for the poor sensitivity of thallium naging are limitations of imaging hardware and ge- metry,[3,15] problems related to redistribution,[16] bal- nced coronary lesions,[17] the effects of drugs on thalli- m uptake,[18,19] the technique of exercise stress,[5] the roblem of overlying myocardial structures or lung[3] and ne lack of a "gold standard" or reference for defining ne angiographic severity of coronary stenoses. Coronary rteriography has several limitations such as marked nterobserver and intraobserver variability in the in- erpretation of results.[20–23]

During the clinically silent period of developing oronary atherosclerosis, stenotic lesions have complex ffects on pressure and flow in the coronary circulation nat fall into one or more of three categories: (1) reduced patial or regional coronary flow reserve,[17,24,25] (2) re- uced subendocardial-subepicardial perfusion ra- os,[26–33] and (3) reduced perfusion pressure due to the decrease in pressure across the stenosis, particularly at high coronary flow rates under stress.[34,35] Although this decreased pressure cannot be directly measured in patients, the physiologic effect of reduced pressure is to reduce subendocardial-subepicardial perfusion ratios. With appropriate application of current myocardial imaging techniques, these pressure-flow effects can be identified as relative perfusion abnormalities indicative of coronary lesions before they become severe enough to cause sudden death, myocardial infarction or angina pectoris.

This study was designed to answer one question: Under idealized experimental conditions, what is the minimal coronary stenosis that can be detected with myocardial perfusion imaging? The results of this study demonstrate a physiologic basis for detecting 40 percent diameter stenoses of coronary arteries with cross-sectional myocardial imaging of regional and epicardial-endocardial perfusion during maximal pharmacologic coronary vasodilatation.



GURE 1. Anatomy of the canine heart **(top)** viewed through a left oracotomy. For cross-sectional myocardial imaging, the heart was moved and cut as shown **(bottom)** into 1 cm thick sections. These ctions were imaged as if one were looking up the long axis of the left ntricle from apex to base. LAD and CIRC = regions supplied by the t anterior descending and circumflex coronary arteries, respec- ely.

Methods

Experimental procedure: Twelve field hounds weighing 30 to 35 kg were anesthetized with 0.5 to 0.8 g of intravenous thiamylal and maintained with methoxyflurane anesthetic gas delivered through a Heidbring vaporizing bottle in line with a Harvard volume respirator attached to a cuffed endotracheal tube. Through a left thoracotomy the left circumflex artery was dissected free for 2 to 3 cm and a snugly fitting, perivascular electromagnetic flowmeter (Zepeda Electronics, Seattle, Washington) was placed on the artery. After an occlusive zero baseline was established, the hyperemic responses to three separate 10 second occlusions were recorded at 10 mm/sec paper speed on an Electronics for Medicine DR-12 physiologic recorder. Just distal to the flow transducer a concentric coronary stenosis was produced by applying 0.5 cm long drilled plastic half blocks to the artery. A steel ball, 3.18 mm in diameter, was then attached to the epicardium just adjacent to the stenosis as a size reference. The hyperemic responses to three separate 10 second occlusions were again recorded. The flow transducer was then removed and small Teflon® catheters (Bard A-cath, 1968-T, 18.5 gauge × 1 1/4 inch [3.1 cm] catheter, New Jersey) were inserted into the left atrium and for 1 to 2 mm into the circumflex coronary artery 1 cm proximal and distal to the stenosis. Mean arterial pressures were recorded through these catheters with a differential pressure transducer (National Semiconductor Corporation, part no. LX1701D, Santa Clara, California) calibrated against 100 mm Hg before, during and after each experiment.

The pressure differential or gradient across the stenosis was recorded during control conditions and during the reactive hyperemia after three separate 10-second occlusions. During control conditions, 10 millicuries (mCi) of indium-113m–labeled human albumin microspheres was then injected into the left atrial catheter. Dipyridamole (Boehringer Ingelheim, Elmsford, New York) was then injected intravenously at a dose rate of 0.6 mg/kg body weight over 4 to 8 minutes. Because intravenous dipyridamole causes a decrease in systemic pressure in anesthetized animals[31,36–39] but not awake unsedated animals (unpublished observation in this laboratory), aortic pressure was maintained at control levels with intravenous metaraminol. Five minutes after completion of the dipyridamole infusion, when maximal coronary vasodilatation was present, 5 mCi of technetium-99m–labeled human albumin microspheres were injected into the left atrial catheter.

Coronary arteriography: Coronary arteriograms of stenoses were then obtained during injection of Hypaque-M®, 75 percent into the proximal coronary catheter while triggering exposure of a single spot film off the electrocardiogram at end-diastole to avoid blurring of the X-ray film during systolic motion. Exposures were at 1/60 second, 200 milliamperes at 70 to 80 kilovolts using fine grain Ultra Detail phosphor Radelein Cassettes and fine grain Ultra Detail, Cronex 7, Dupont X-ray film and a General Electric Maxiray 100 X-ray tube with a 0.6 mm focal spot and a 22 inch (55.9 cm) tube to film distance.

Indocyanine green was injected into the circumflex arterial catheter to separate the distribution of the circumflex artery from the left anterior descending artery. The animals were then sacrificed by injecting potassium chloride into the left atrium. The heart was removed, the atria and right ventricle were trimmed off and discarded. With a slicing jig the left ventricle was then cut into 1 cm thick cross-sectional slices (Fig. 1). Then 50,000 count images of these slices were obtained with an Ohio Nuclear series 100 gamma camera with a pin hole collimator at 390 kev for indium-113m and at 140 kev for technetium-99m, each with a 15 percent window (full width half maximum). Scintillation data were stored in a Medical Data Systems Nova II miniprocessor adapted for nuclear medicine applications.

Coronary arteriograms were enlarged five times on medium contrast photographic printing paper and the stenosis was drawn in with a fine pencil. The contours of the stenosis were then traced on a Tektronix model 4953 digitizing tablet on line with a PDP 11/45 computer for automatic quantitative analysis as previously described.[40] The computer printout of this quantitative analysis gave the percent diameter narrowing and percent cross-sectional area reduction of each stenosis.

Results

Figure 1 shows the anatomy of a cross-sectional slice of the canine left ventricle viewed as if looking up the long axis of the ventricle from apex to base. In this view the cross section resembles a doughnut with a ring of myocardium and a central hole, which is the ventricular cavity. The anterior papillary muscle appears as a thickening in the upper aspect of the myocardial ring and is supplied predominantly by the left anterior descending coronary artery. The posterior papillary muscle appears as a thickening in the lower right aspect of the myocardial ring and is supplied by the circumflex coronary artery.

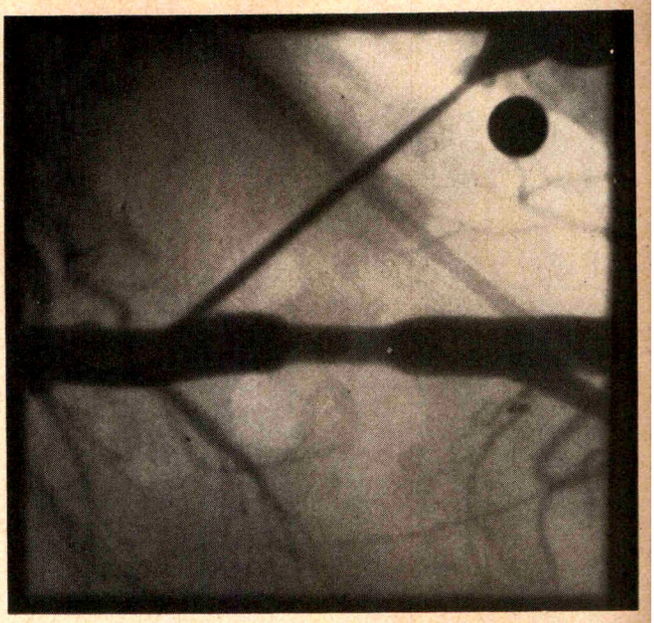


FIGURE 2. Coronary arteriogram showing a 40.8 percent diameter stenosis as measured by computerized quantitative coronary arteriographic analysis. The steel ball size marker next to the stenosis is 3.18 mm in diameter.

Figure 2 shows a coronary arteriogram of a coronary stenosis causing a 41 percent diameter narrowing of the coronary artery. Figure 3 shows for this stenosis the corresponding computer-regenerated myocardial image of flow distribution during resting control conditions and during maximal coronary vasodilation after administration of dipyridamole. At rest, regional and transmural perfusion was normal. After dipyridamole transmural perfusion was markedly abnormal with the subendocardium perfused much less than the subepicardium in the distribution of the stenotic circumflex coronary artery. There was also a modest decrease in the

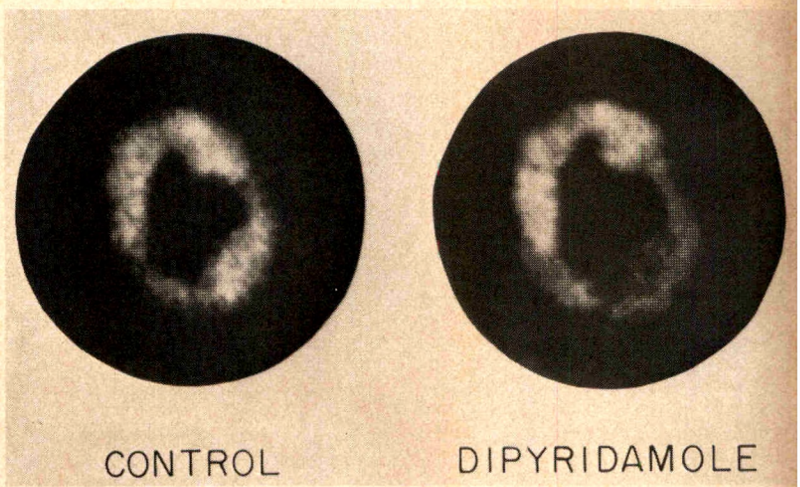


FIGURE 3. Myocardial image of perfusion in a cross-sectional slice during resting control conditions and during maximal coronary vasodilation induced with intravenous dipyridamole. There is no background subtraction or computer manipulation of these regenerated images.

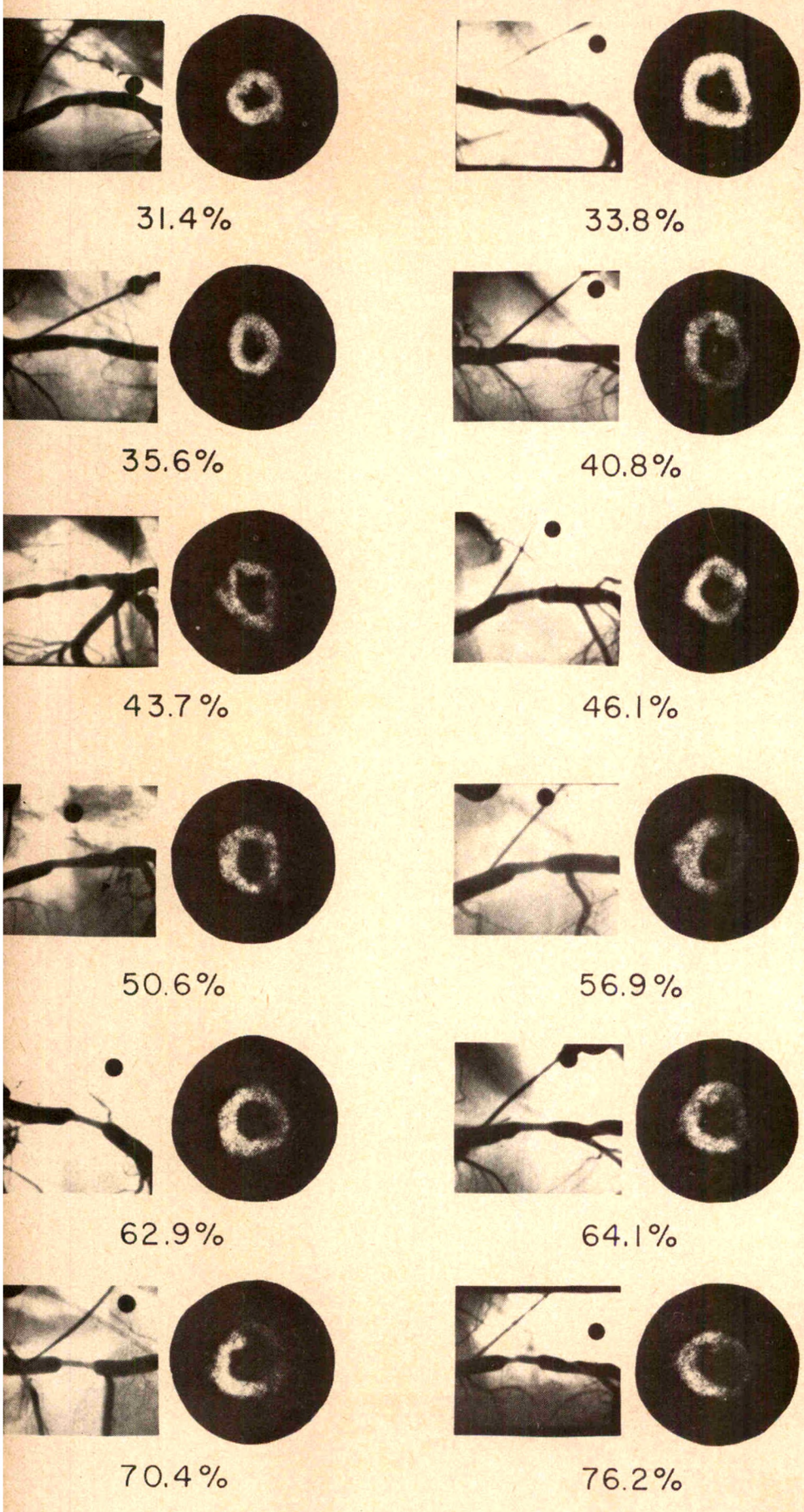


FIGURE 4. Coronary arteriograms and corresponding cross-sectional myocardial perfusion images for stenoses ranging from 31.4 to 76.2 percent diameter narrowing as determined with computerized quantitative coronary arteriography. Original Polaroid scintiphotographs of images are shown.

epicardial perfusion in the circumflex distribution relative to the distribution of the anterior descending coronary artery. There was no background subtraction from these images or those shown subsequently.

Figure 4 shows the arteriograms of coronary stenoses ranging from 31.4 to 76.2 percent diameter narrowing as determined from computerized quantitative analysis of each arteriogram. It also shows the original Polaroid scintiphotographs of cross-sectional myocardial perfusion after dipyridamole for each of the stenoses shown.

Table I summarizes the findings. Coronary stenoses of 36 percent or less diameter narrowing caused borderline or no abnormalities on images of cross-sectional myocardial perfusion at maximal coronary vasodilation after dipyridamole. In some of these images the papillary muscle supplied by the stenotic left circumflex coronary artery appeared to be underperfused relative to the papillary muscle supplied by the left anterior descending coronary artery. However, because there was no definite subendocardial underperfusion of the free posterior left ventricular wall, these images were interpreted conservatively as borderline or normal. Coronary stenoses of 41 to 51 percent diameter narrowing caused a definite decrease in subendocardial perfusion relative to the subepicardium and relative to the normally perfused subendocardium. There was also a mild decrease in epicardial perfusion in the circumflex distribution relative to the epicardium of the nonstenotic left anterior descending artery. Coronary stenoses of 57 percent or greater diameter narrowing caused a marked fall in transmural regional perfusion relative to the nonstenotic left anterior descending coronary artery, and this relative underperfusion was most severe in the endocardium.

TABLE I
Relation Between Severity of Coronary Stenosis and Abnormal Cross-Sectional Myocardial Images

Stenosis % Diameter	Stenosis % Area	Control Resting Image	Image Defect After Dipyridamole
31.4	50.3	Normal	None
33.8	56.2	Normal	None
35.6	58.5	Normal	None
40.8	65.1	Normal	Subendocardial
43.7	68.3	Normal	Subendocardial
46.1	70.9	Normal	Subendocardial
50.6	75.7	Normal	Subendocardial
56.9	81.4	Normal	Transmural
62.9	86.3	Normal	Transmural
64.1	87.2	Normal	Transmural
70.4	91.3	Normal	Transmural
76.2	94.3	Normal	Transmural

Discussion

Angiographic severity of coronary stenoses causing myocardial perfusion defects: Our results demonstrate that coronary stenoses of 40 percent diameter narrowing can be detected with myocardial imaging under idealized experimental conditions utilizing a coronary vasodilator, an imaging agent taken up in the myocardium in proportion to flow and cross-sectional imaging of endocardial-epicardial perfusion. Previous studies[26,27,30–33,36] have demonstrated that the subendocardium is more susceptible than the epicardium to underperfusion and ischemia. However, these studies utilized tissue counting techniques and did not determine the severity of the stenoses. Therefore, it is not possible to extrapolate previous results to intact animals or patients studied with perfusion imaging and coronary arteriography. Our study provides experimental data on the angiographic severity of stenoses causing cross-sectional perfusion defects. Although percent diameter stenosis is not the sole determinant of hemodynamic consequences, the stenoses produced in our study were all of the same length and comparable geometry. The relative hydraulic severity of these stenoses are therefore adequately described by percent stenoses. Similar perfusion abnormalities would be expected with less severe but longer lesions or several lesions in series. Thus, our results are directly applicable to clinical coronary arteriography only if all the geometric characteristics of the stenosis are taken into account by quantitative coronary arteriography.[40]

Physiologic requirements for clinical application of method to assess coronary flow reserve: It is appropriate to ask whether the idealized conditions of our study can be obtained with available noninvasive techniques applicable to man. The first physiologic requirement is a potent stimulus for increasing coronary flow as previously described.[17,25,35,41–48] The rationale for using coronary vasodilators is best described in terms of the diagram in Figure 5, representing the stenotic coronary artery and distal coronary vascular bed as two resistances in series as demonstrated by Shipley and Gregg.[49] If the distal bed resistance (R_b) is zero, the system behaves like an open tube and any degree of stenosis reduces the flow. If the distal bed resistance is high, it is the dominant factor controlling flow and the stenosis may become progressively severe without having an effect until stenotic resistance approaches that of the distal vascular bed. Coronary vasodilators convert the normally low flow, high resistance coronary circulation at rest into a high flow, low resistance system in which the stenoses have greater effects on relative flow and regional perfusion as shown by the dashed line in the diagram.

Bookstein and Higgins[50] studied the relative effectiveness of various coronary vasodilators for diagnostic purposes and concluded that intracoronary adenosine triphosphate infusion (with or without papaverine) and intravenous dipyridamole are the most potent coronary vasodilators available. In addition, the effect of intravenous dipyridamole on the coronary circulation (1) can be closely regulated by adjusting the dose rate of infusion,[35,48] (2) can be instantaneously reversed with intravenous aminophylline, a dipyridamole antagonist,[31,51–55] (3) does not increase myocardial oxygen demands as much as exercise,[38,39,56–58] and (4) does not invoke myocardial ischemia as such as a diagnostic end point and therefore permits the greatest regional per-

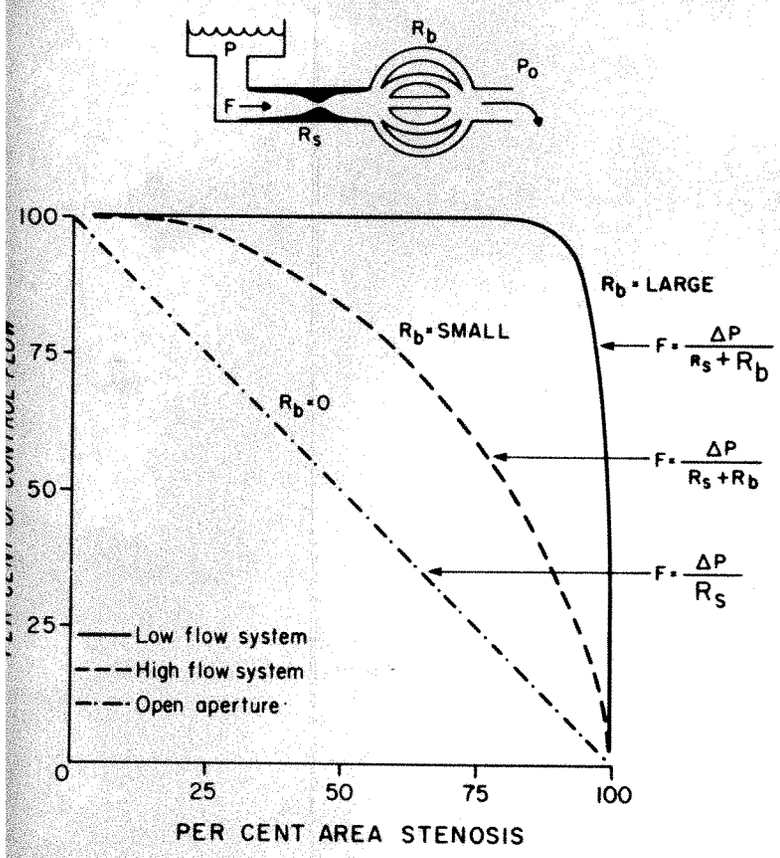


FIGURE 5. Diagram representing the diseased coronary circulation as two resistances in series—the stenosis (R_s) and distal vascular bed (R_b). The effects of reducing R_b with vasodilators is shown by the **dashed line.** The equations at right show the relation between resistance and flow (F). For a given total pressure gradient across the stenosis and distal vascular bed (ΔP), flow is determined primarily by R_b if R_b is large. P = arterial pressure; P_0 = venous pressure. Increments in the value of stenotic resistance (R_s) have little effect until R_s approaches the value of R_b. When R_b is zero, R_s completely determines flow.

usion abnormalities for imaging purposes before ischmia develops. This stimulus may therefore be more eadily controlled than exercise stress and is not subject o the effects on treadmill testing of motivation, chronic ung disease and peripheral vascular or musculoskeletal npairment.

The second physiologic requirement of a method for ssessing coronary flow reserve is that the myocardial ptake of the imaging agent be proportional to flow at igh coronary flow rates of at least four or more times esting levels. An agent whose uptake is not related to ow will be insensitive for detecting mild stenoses, and n agent whose myocardial uptake is linearly related to ow will be the most sensitive.[35] For example, the iyocardial uptake of thallium-201 is linearly proporonal to flow at resting control levels down to ero,[3,15,16,19] but at higher flow levels necessary to assess oronary flow reserve thallium uptake is not proporonal to flow.[15,19] Thallium uptake may also be affected y metabolic factors influencing membrane transport nd intracell trapping independent of perfusion. Acordingly, perfusion imaging with thallium is less sentive for detecting coronary stenoses than perfusion naging with labeled albumin particles that are deosited in the myocardium in proportion to flow.[35] A ypothetical ideal imaging agent would be injected inavenously, be completely and rapidly extracted by the iyocardium at high as well as low coronary flow rates nd be mechanically or metabolically trapped in the iyocardium where it would remain without recirculation or clearance for the period of data acquisition[59]; it should have a short half-life so that repeated studies can be carried out.

Clinical implication: An agent that may approximate these characteristics is intravenously administered nitrogen-13 ammonia, a cyclotron-produced positron emitter with a half-life of 10 minutes.[60–65] With this agent cross-sectional emission computer tomography may also be carried out.[66–70] The application of these techniques for the noninvasive identification of mild coronary stenoses in animals and man will be described in subsequent reports. This study utilized optimized ideal experimental techniques to identify the minimal coronary stenosis detectable with a potent coronary vasodilator, an imaging agent taken up by the myocardium in proportion to flow and cross-sectional myocardial perfusion imaging. Whether comparable sensitivity can be achieved with noninvasive techniques in vivo remains to be determined.

Acknowledgment

I acknowledge the superb laboratory work of Dennis Lee, Kathy Lovgren, Ann Coleman and Zdenka Gruenbaum, and the assistance of Steven Larson, MD, in preparing indium-113m–labeled human albumin microspheres. The indium generator was obtained from New England Nuclear, N. Billerica, Massachusetts and human albumin microspheres were obtained from the 3M Company, St. Paul, Minnesota. Intravenous dipyridamole was kindly provided by Wolf Michaelis, MD and Wilbur Bensen, MD of Boehringer Ingelheim, Inc., Elmsford, New York.

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Effect of Propranolol and Nitroglycerin Plus Methoxamine on Transmural Creatine Kinase Activity After Acute Coronary Occlusion

GARY J. JESMOK, PhD
GARRETT J. GROSS, PhD
HAROLD F. HARDMAN, MD, PhD

Milwaukee, Wisconsin

Transmural creatine kinase activity was determined 5 hours after acute occlusion of the left anterior descending coronary artery in 27 open chest anesthetized dogs. In seven dogs, propranolol, 2 mg/kg, was given intravenously over a 10 minute period 10 minutes after occlusion. In 10 dogs, nitroglycerin, 300 μg/min, was infused intravenously for 1 hour 10 minutes after occlusion. Methoxamine, 300 to 500 μg, was administered to return blood pressure and heart rate to prenitroglycerin levels. In untreated dogs, there was a distinct transmural gradient of creatine kinase activity in the ischemic region from subepicardium to subendocardium: nonischemic subepicardium 1,187 ± 50 international units (IU)/g versus ischemic subepicardium 1,054 ± 46 IU/g and nonischemic subendocardium 1,170 ± 53 IU/g versus ischemic subendocardium 766 ± 42 IU/g, respectively. Administration of propranolol did not affect the transmural creatine kinase gradient after 5 hours of occlusion. In contrast, nitroglycerin plus methoxamine significantly ($P < 0.05$) decreased subendocardial creatine kinase depletion after 5 hours of occlusion (776 ± 42 versus 978 ± 47 IU/g). These findings demonstrate the unique capability of nitroglycerin plus methoxamine to protect the subendocardium during ischemic insult.

Cell death in the myocardium after coronary arterial occlusion develops first in the severely ischemic subendocardium and evolves progressively to include areas of moderately ischemic mid and subepicardium.[1] Although studies[2–6] have shown that eventual infarct size can be attenuated with early pharmacologic intervention, little work has been done on the discrete transmural areas of the myocardium that may be protected from ischemic injury by these various therapeutic agents. In this study, two pharmacologic interventions that have been demonstrated to reduce infarct size—propranolol, and nitroglycerin plus methoxamine[7,8]—were examined for their ability to protect against depletion of creatine kinase (CK) in ischemic subepicardial and subendocardial myocardium after 5 hours of coronary arterial occlusion. This index was utilized because it has been demonstrated that myocardial CK concentration decreases in proportion to the severity of ischemic damage.[9,10]

Methods

Experimental preparation: Adult mongrel dogs of either sex, weighing between 19 and 27 kg, were fasted overnight, anesthetized with sodium pentobarbital (30 mg/kg, intravenously), intubated and ventilated with a respirator (Harvard Model 607) with room air at 10 to 15 breaths/min. Atelectasis was prevented by maintaining an expiratory pressure of 5 to 7 cm of water with a trap. Arterial blood pH was maintained between 7.35 and 7.45 with an intravenous infusion of 1.5 percent bicarbonate when necessary.

From the Department of Pharmacology, Medical College of Wisconsin, Milwaukee, Wisconsin. This study was supported by Research Grant HL 08311 from the U. S. Public Health Service, Bethesda, Maryland, and the Deborah Hospital Foundation, Browns Mills, New Jersey. Manuscript received April 3, 1978; revised manuscript received June 27, 1978, accepted June 28, 1978.

Address for reprints: Gary Jesmok, PhD, Department of Pharmacology, Medical College of Wisconsin, Box 26509, Milwaukee, Wisconsin 53226.

Arterial blood pressure was recorded by means of a catheter nserted into the right femoral artery, advanced to the thoracic orta and attached to a strain gauge pressure transducer Statham P23AC). The right femoral vein was catheterized or drug and sodium bicarbonate administration. Left ventricular pressure was determined by means of a pressure ransducer-tipped catheter(Millar PC380; no. 8F) passed by ray of the left carotid artery into the left ventricle. Left ventricular rate of rise of pressure (dP/dt) was obtained by electronic differentiation of the left ventricular pressure pulse. Heart rate was determined from the electrocardiogram (lead I).

A left thoracotomy was performed at the fifth intercostal pace, the lung gently retracted and the heart suspended in pericardial cradle. The anatomy of the left anterior descending coronary artery was visually examined, and only dogs xhibiting a similar anatomic distribution of this vessel were sed in the experiments. After the surrounding tissue was issected away, a ligature was placed around the left anterior escending coronary artery just below the first major diagonal ranch. The vessel was occluded for approximately 20 seconds o verify whether cyanosis appeared distal to the occlusion. cyanosis did not occur the animal was also excluded from ne study. These precautions were taken because it has been emonstrated[11,12] that there is considerable variability in chemic bed size and collateral flow among dogs even when ne point of coronary ligation is similar in each animal. With nese precautions, in conjunction with the number of animals each experimental group, it was believed that any coronary ow variations would be evenly distributed among the roups.

In animals selected for study, heparin (500 units/kg, intravenous) was administered before occlusion. The electrocardiogram, mean arterial blood pressure, left ventricular systolic and end-diastolic pressures and dP/dt were continuously recorded on a Grass model 7 polygraph during the 5 our occlusion period.

Protocol: A total of 27 dogs were utilized in the study. Animals were selected for a control group (10 dogs), treatment with propranolol (7 dogs) and treatment with nitroglycerin plus methoxamine (10 dogs) in a random fashion. In the propranolol-treated group, the drug (2 mg/kg, intravenously) was administered 10 minutes after occlusion and infused over 10 minutes. After the procedure of Capurro et al.,[13] treatment with nitroglycerin and methoxamine was begun 10 minutes after occlusion and continued for 1 hour. Nitroglycerin (300 μg/min) was administered with a constant intravenous infusion. Methoxamine was administered intravenously in 300 to 500 μg bolus injections as needed to return mean arterial blood pressure to prenitroglycerin levels, thus preventing reflex tachycardia.

In all three groups, the left anterior descending coronary artery remained occluded for 5 hours. After 5 hours, the animals were killed with a lethal dose of pentobarbital, and the hearts were rapidly removed and immediately placed in cold isotonic saline solution. The region supplied by the occluded left anterior descending coronary artery was delineated by visual inspection. This procedure was facilitated by noticeable cyanosis of the ischemic area served by the ligated artery. Two tissue samples, each weighing 2 to 3 g, were taken from the apparent center of the ischemic region. Care was taken to sample the identical area in the three experimental groups of dogs. Duplicate tissue samples were also taken from the normally perfused posterior base of each heart. The tissue samples were washed in chilled saline solution, bisected into subepicardial and subendocardial sections and stored at −20° C until they were assayed for their content of CK activity, which was chosen as a marker of cell viability.

Tissue creatine kinase activity: CK was analyzed by the method of Kjekshus and Sobel.[9] The myocardial samples were weighed, minced with scissors and homogenized in 10 vol/g of iced 0.25 molar sucrose, 0.1 molar Tris buffer (pH 7.4), containing 1 mm EGTA and 1 mm mercaptoethanol in a Waring blender (model 1120) for 2 minutes. The homogenates

ABLE I

ummary of Hemodynamic Data From Control Group and Groups Treated With Propranolol and With Nitroglycerin Plus ethoxamine (mean ± standard error of the mean)

	Hours After Ligation					
	0	1	2	3	4	5
	Control Group (no. = 10)					
HR	165 ± 7	168 ± 5	168 ± 8	170 ± 6	167 ± 9	172 ± 6
MABP	128 ± 7	129 ± 6	125 ± 7	125 ± 8	127 ± 9	115 ± 11
LVEDP	0.7 ± 1.1	3.0 ± 1.4*	3.5 ± 1.2*	3.5 ± 1.8*	4.0 ± 8*	5.0 ± 2.4*
LVSP	150 ± 11	147 ± 10	148 ± 12	147 ± 10	145 ± 11	135 ± 12
dP/dt	2,470 ± 244	2,310 ± 201	2,380 ± 169	2,260 ± 181	2,178 ± 161	2,243 ± 225
	Group Treated With Propranolol (2 mg/kg, no. = 7)					
HR	160 ± 8	133 ± 9*	140 ± 8*	133 ± 10*	132 ± 11	136 ± 13*
MABP	133 ± 8	115 ± 7*	113 ± 9*	117 ± 10*	114 ± 7*	112 ± 10*
LVEDP	1.2 ± 8	4.2 ± 2.2*	5.0 ± 2.3*	4.6 ± 1.9*	5.1 ± 2.0*	4.9 ± 2.9*
LVSP	155 ± 13	132 ± 10*	133 ± 8*	135 ± 11*	127 ± 9*	131 ± 7*
dP/dt	2,388 ± 215	1,897 ± 237*	1,934 ± 246*	1,919 ± 281*	1,819 ± 256*	1,841 ± 257*
	Group Treated With Nitroglycerin Plus Methoxamine (300 μg/min, no. = 10)					
HR	162 ± 6	147 ± 8	148 ± 9	152 ± 6	153 ± 8	147 ± 7
MABP	126 ± 8	118 ± 7	121 ± 8	120 ± 7	120 ± 7	122 ± 8
LVEDP	1.4 ± 1.0	3.9 ± 1.6*	5.1 ± 2.0*	4.9 ± 2.4*	4.8 ±2.3*	5.0 ± 2.2*
LVSP	144 ± 10	135 ± 6	139 ± 11	140 ± 9	138 ± 8	139 ± 7
dP/dt	2,461 ± 232	2,209 ± 199	2,250 ± 235	2,179 ± 203	2,204 ± 212	2,240 ± 227

* Denotes significant difference ($P < 0.05$ by paired comparison) from zero time values in each group. Values at zero time refer to measurements ade before occlusion and treatment. Both drug interventions were performed 10 minutes after occlusion. Propranolol was given over a 10 minute riod; nitroglycerin plus methoxamine was administered for 1 hour.
dP/dt = rate of rise of left ventricular pressure (mm Hg/sec); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm); LVSP = left ventricular systolic pressure (mm Hg); MABP = mean aortic blood pressure (mm Hg).

were then centrifuged at 17,000 × *g* for 15 minutes. The supernatants were diluted (1:500) in a 0.01 molar Tris buffer (pH 7.4). The CK activity was measured spectrophotometrically at 25° C, using the method of Rosalki.[14] The reaction was started by the addition of 0.10 ml of diluted supernatant to the cuvettes, which contained 3 ml of reaction mixture. The CK activity is expressed in international units (IU) per gram wet tissue weight at 25° C using a temperature correction factor[14] or in percent of CK activity found in the control samples of the normal myocardium taken from the posterior base of the left ventricle. All enzyme assays were performed in duplicate.

Because the two separate subepicardial and subendocardial tissue samples from the ischemic and nonischemic regions did not significantly differ in CK content, these samples, even though assayed separately, were combined for statistical and graphic presentation. Thus, four distinct tissue groups are summarized: subepicardium and subendocardium from the normal region and subepicardium and subendocardium from the apparent center of the ischemic region.

Data are expressed as mean ± standard error of the mean and were statistically analyzed by group and paired comparisons. All drugs were dissolved in a 0.9 percent sodium chloride solution.

Results

Hemodynamic data: The hemodynamic data from the three experimental groups are summarized in Table I. In the control group, coronary arterial ligation had little effect on the hemodynamic variables recorded. There was a significant ($P < 0.05$) elevation of left ventricular end-diastolic pressure over the 5 hours of occlusion.

Propranolol (2 mg/kg, intravenously) produced a significant ($P < 0.05$) decrease in heart rate, mean arterial blood pressure, left ventricular systolic pressure and dP/dt. The elevation of left ventricular end-diastolic pressure was similar to that seen in the control series.

In the group treated with nitroglycerin plus methoxamine, only left ventricular end-diastolic pressure was significantly elevated during the 5 hour period of occlusion.

Transmural CK activity: Table II summarizes the transmural CK activity in ischemic and nonischemic regions of the myocardium after 5 hours of occlusion of the left anterior descending coronary artery. In all three experimental groups, there was a homogeneous transmural distribution of CK activity in the nonischemic region (posterior base) of the myocardium after 5 hours of occlusion: subepicardium 1,182 ± 42, subendocardium 1,164 ± 52 IU/g (54 tissue samples). There were no significant differences among groups in the nonischemic regions.

In the ischemic regions, both subepicardium and subendocardium exhibited diminished CK activity after 5 hours of occlusion of the left anterior descending coronary artery. Although there was a significant ($P < 0.05$, paired comparison) decrease in tissue CK activity in the ischemic subepicardium within all three groups, no difference from the ischemic control value was observed in the groups treated with propranolol or with nitroglycerin plus methoxamine. The ischemic injury as reflected by subepicardial CK depletion at 5 hours of occlusion was not extensive (depletion averaged 10 to 11 percent in all three experimental groups).

In contrast, ischemic subendocardial CK depletion at 5 hours in the control group was substantial. In the ischemic subendocardium, CK activity decreased from a nonischemic control value of 1,170 ± 53 to 766 ± 42 IU/g ($P < 0.001$ by paired comparison). CK depletion in the ischemic subendocardial region in the propranolol treated group was not significantly different from that in the control group, whereas nitroglycerin plus methoxamine significantly diminished ischemic subendocardial CK depletion. In the group treated with nitroglycerin plus methoxamine, ischemic subendocardial CK activity decreased from a control nonischemic value of 1,151 ± 43 to only 978 ± 47 IU/g ($P < 0.05$ group comparison with control). The protection afforded by nitroglycerin plus methoxamine to the ischemic subendocardium during acute coronary occlusion is illustrated in Figure 1. Whereas the control and pro-

TABLE II

Transmural Creatine Kinase (CK) Activity After 5 Hours of Acute Coronary Occlusion (mean ± standard error of the mean)

Group	CK Activity (IU/g at 25° C)			
	Nonischemic Region		Ischemic Region	
	Subepicardium	Subendocardium	Subepicardium	Subendocardium
Control (no. = 10)	1,187 ± 50	1,170 ± 53	1,054 ± 46	766 ± 42
Propranolol (no. = 7)	1,148 ± 38	1,173 ± 66	1,023 ± 48	807 ± 65
Nitroglycerin + methoxamine (no. = 10)	1,213 ± 39	1,151 ± 43	1,083 ± 36	978 ± 47*

* Significantly different ($P < 0.05$) from value in control subendocardial ischemic region.

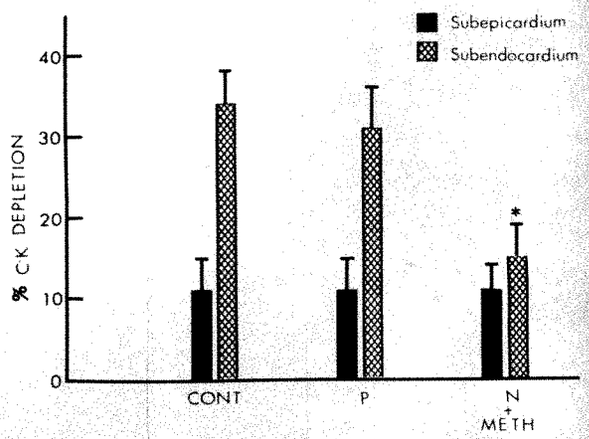


FIGURE 1. Effect of treatment with propranolol (P) and nitroglycerin plus methoxamine (N + METH) on the percent depletion of subepicardial and subendocardial creatine kinase (CK) activity after 5 hours of coronary occlusion. * $P < 0.05$ versus control (CONT) subendocardial ischemic region.

ranolol-treated groups averaged between 30 and 34 ercent depletion of tissue CK activity in the ischemic ubendocardium (compared with 10 to 11 percent in the ubepicardium), ischemic subendocardial CK depletion vas less than 15 percent in the group treated with nitroglycerin plus methoxamine. Thus, treatment with itroglycerin and methoxamine significantly decreased ubendocardial ischemic injury as measured from tissue K depletion after 5 hours of acute coronary occlusion.

Discussion

Vulnerability of subendocardium versus subepicardium to ischemic injury: In agreement with others,[9,15] we found no transmural gradient in creatine inase (CK) activity in the nonischemic region of the yocardium. However, there was a highly significant ransmural gradient of CK activity in the ischemic region after 5 hours of coronary occlusion. A threefold reater tissue CK depletion occurred in the ischemic ubendocardium. It is apparent from the transmural CK alues in our study that the subendocardium is subject greater ischemic injury than the subepicardium after oronary occlusion. This finding is consistent with the ata of several investigators[1,9,15,16] and that of a variety f studies demonstrating increased subendocardial ulnerability during coronary occlusion.[17,18] The vulerability of the subendocardium appears to be partly result of the maldistribution of blood flow that occurs fter coronary occlusion.

The vascular reserve of the subendocardium is limed by the mechanics of subendocardial blood flow. uring systole, intramyocardial pressure in the inner yers of the heart equals or exceeds aortic pressure; nsequently arterial flow in the deeper myocardium curs mainly during diastole.[19] Because transmural ood flow is normally homogeneous, flow is most likely aintained by either a greater vascularity or a preferitially greater vasodilation of vessels, or both, in the ner layers of the myocardium during diastole.[20] uring ischemia induced by coronary occlusion, arteoles in all layers of the myocardium become maximally lated, flow becomes pressure-dependent and the adient of vascular resistance, which is partially reonsible for preferential blood flow to the subendordium in diastole, is lost.[17,18,20] Pressure distal to the clusion decreases while intramyocardial pressure mains the same or increases because of an elevated left ntricular end-diastolic pressure; thus there is a serely depressed pressure gradient in the subendocarum by which flow is to be maintained. Consequently, llateral flow to the ischemic myocardium is diminhed to a greater extent in the subendocardium than the subepicardium.

Other factors contribute to or exacerbate the maldistribution of blood flow during ischemia. It has been monstrated that, after coronary occlusion, resistance flow in the subendocardial infarcting tissue increases d causes a redistribution of flow to the adjacent bepicardium.[16] Thus, after a decrease in coronary flow, subepicardial flow is maintained, whereas subendocardial flow is diminished.[16,17]

Furthermore, it has been demonstrated that oxygen consumption in the subendocardium exceeds that in the subepicardium.[21] This further exacerbates the imbalance between oxygen supply and demand in the subendocardium, leading to cell death. Thus, the oxygen supply/demand balance, critical to determining the extent of the jeopardized tissue, is clearly heterogeneous in the left ventricle, and the subendocardium is the most vulnerable.

Effect of propranolol on subendocardial ischemic injury: Propranolol, a pharmacologic agent that has been shown to diminish myocardial necrosis,[22–24] did not affect the extent of ischemic subendocardial CK depletion after 5 hours of coronary occlusion. These results are consistent with data from the recent investigation by Rasmussen et al.[7] They demonstrated that propranolol limits the progression of ischemic damage (eventual infarct size) by preventing necrosis of the moderately ischemic subepicardium peripheral to the central core of the infarct, which is subendocardial. In our experiments 5 hours of occlusion of the left anterior descending coronary artery diminished subepicardial CK activity only 10 percent in the ischemic region, which indicates rather unextensive tissue injury. It may be that a decrease in tissue CK activity of this magnitude is insufficient to demonstrate the protective effect of treatment with propranolol. It does appear that propranolol is not capable of protecting the ischemic subendocardium from necrosis after 5 hours of coronary occlusion.

Effect of nitroglycerin plus methoxamine on subendocardial ischemic injury: In contrast to propranolol, the administration of nitroglycerin plus methoxamine was able to diminish subendocardial ischemic injury as reflected by tissue CK activity after 5 hours of left anterior descending coronary occlusion. Previous work[25] has demonstrated a salutary effect of infusion of nitroglycerin plus methoxamine on ischemic injury, with reduced S-T segment elevation after coronary occlusion. In addition, S-T elevation 10 minutes after occlusion and subsequent myocardial creatine kinase depletion adjacent to each intramyocardial electrode 24 hours later were lessened after administration of nitroglycerin plus methoxamine.[26,27] The mechanism by which nitroglycerin plus methoxamine preserves jeopardized subendocardial tissue was suggested by the recent work of Capurro et al.,[13] who found a threefold increase in subendocardial blood flow after a 1 hour infusion of nitroglycerin plus methoxamine. This increase in subendocardial blood flow was maintained for 5 hours. More recently, Chiariello et al.[28] found that methoxamine produced a large increase in collateral blood flow that resulted in a decrease in ischemic injury. Thus, the mechanism of the salutary effect of nitroglycerin plus methoxamine on subendocardial ischemic injury is most likely related to an augmentation of collateral blood flow.

Because infarction of the subendocardium is the

consequence of an imbalance in oxygen supply and demand, other factors may be involved in the ability of nitroglycerin plus methoxamine to reduce ischemic injury. Nitroglycerin, by diminishing left ventricular filling pressure even in the presence of methoxamine, decreases myocardial wall tension, thereby decreasing myocardial oxygen requirements.[27] Furthermore, decreased wall tension may also reduce intramural coronary arterial compression and contribute to the increase in collateral flow.[8] Thus, the beneficial effects of nitroglycerin and methoxamine in reducing subendocardial ischemic injury may involve several effects of the drugs on the multiple determinants of myocardial oxygen supply and demand.

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Origin of So-Called Right and Left Ventricular Arrhythmias in Acute Myocardial Ischemia

ELIESER KAPLINSKY, MD
SATOSHI OGAWA, MD
JAMES KMETZO
LEONARD S. DREIFUS, MD, FACC

Philadelphia, Pennsylvania

The anatomic origin of ventricular arrhythmias occurring immediately after coronary arterial ligation was studied in 32 dogs. The electrocardiogram and seven single or composite bipolar electrograms were recorded from various sites within and surrounding the ischemic area in the left and right ventricles. Delay and fragmentation in the activation of the epicardial ischemic zone of the left ventricle, bridging diastole, preceded the appearance of ventricular arrhythmias and were continuous during the rhythm disorders. So-called left and right ventricular arrhythmias were associated with similar delay and fragmentation in left ventricular ischemic epicardial activity. Multiple and simultaneous activation of both the right and left ventricles produced ventricular fusion premature complexes. Multiple exit points increased before ventricular fibrillation occurred. The ultimate origin of premature ectopic impulse formation in the ventricles is not necessarily related to one or more exit points in either ventricle. Ischemic damage to the heart produces ventricular arrhythmias that appear to originate from both ventricles. The site of origin of ventricular arrhythmias should not be the sole factor in assessing the benign or malignant properties of the arrhythmia.

The importance of ventricular premature complexes both as a prognostic risk factor and as a carrier of risk of sudden death to the patient with acute myocardial ischemia has been documented in many studies.[1–4] However, because of the abundance of ventricular premature complexes both in patients with cardiac disease and in the normal population,[5–7] it is essential to differentiate between the benign form of ventricular ectopic activity and the more ominous form. Such a distinction is plausible because many studies have shown that extremely early, repetitive and multifocal ventricular premature complexes are more dangerous than those that are rare, occur late in the cardiac cycle and are of uniform configuration.[2,3,7–11]

Attempts have also been made to distinguish between "benign" and "malignant" ventricular premature complexes on the basis of their anatomic origin in the belief that ectopic beats arising from the left ventricle are more suggestive of heart disease than are those of right ventricular origin.[12–16] The greater prevalence of right ventricular premature complexes among young and healthy persons seems to support this assumption. However, patients with proved coronary artery disease have been shown to have ectopic premature complexes and tachycardia originating in the right ventricle.[16,17] Furthermore, ventricular tachycardia may arise from either ventricle in patients with acute myocardial infarction.[18] A low energy, direct current electric shock was shown to change the configuration of ventricular tachycardia in acute myocardial infarction from a right to a left bundle branch block pattern, and vice versa.[19]

Our study was designed to identify the origin of ventricular arrhythmias associated with acute myocardial ischemia in the experimental

From the Departments of Medicine, Jefferson Medical College of the Thomas Jefferson University and the Lankenau Hospital, Philadelphia, Pennsylvania. Manuscript received April 25, 1978; revised manuscript received June 13, 1978, accepted June 14, 1978.
Address for reprints: Elieser Kaplinsky, MD, The Lankenau Hospital, Lancaster and City Line Avenues, Philadelphia, Pennsylvania 19151.

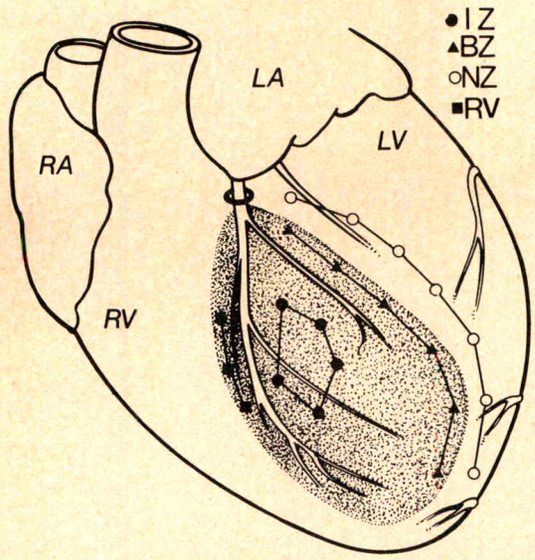


FIGURE 1. Diagrammatic representation of the left anterior surface of the canine heart. **Circle** denotes the ligature around the left anterior descending coronary artery, and the **shading** indicates the resultant ischemic area. Electrodes were placed at endocardial and epicardial sites. Only endocardial electrodes were positioned in the right ventricular (RV) sites. Connecting lines indicate the grouping of composite electrodes. Seven such groupings were obtained—one from the right ventricular endocardial site and two from each of the left ventricular (LV) sites (one endocardial and one epicardial group). BZ = border zone; IZ = ischemic zone; LA = left atrium; NZ = normal zone; RA = right atrium.

animal and to correlate the electrophysiologic changes leading to the emergence of these rhythm disorders with their site of exit.

Methods

The study was performed immediately after coronary arterial ligation in 32 dogs weighing 18 to 30 kg. The animals were anesthetized with the intravenous administration of 30 mg/kg body weight of sodium pentobarbital. Respiration was maintained with a Harvard room air respirator by means of a cuffed endotracheal tube. The chest was opened through the fourth left intercostal space and the heart exposed and suspended in a pericardial cradle. The left anterior descending coronary artery was dissected and a loose ligature positioned around the vessel 1 to 2 cm distal to its origin.

Electrophysiologic studies: Close bipolar Teflon®-coated plunge electrodes were positioned at various epicardial and endocardial points in and around the expected ischemic zone in both the right and left ventricles. In 14 dogs, the recordings were made from composites of groups of bipolar electrodes (Fig. 1). In the other 18 dogs, the electrodes were positioned over a wide area of the infarcted and normal zones of both ventricles. All data were recorded on an eight channel Hewlett-Packard photographic recorder or photographed from the face of a Tektronics 5115 storage oscilloscope. Lead II of the electrocardiogram (at 0.5 to 200 cycles/sec) and seven electrograms (at 50 to 1,000 cycles/sec) from single bipolar or composite groups of bipolar electrodes were recorded in each experiment. Before ligation of the coronary artery, various sites in the left and right ventricles were stimulated to determine whether the activation sequence, as recorded from the bipolar plunge electrodes, could identify the actual stimulated site.

The left anterior descending coronary artery was then ligated in one stage. Recordings were obtained in each animal at paper speeds of 100, 200 and 500 mm/sec.

Definition of terms: Ventricular ectopic complexes were defined on the basis of initial activation as follows: (1) *Left ventricular complex:* The initial distinct activation was in the left ventricle and clearly preceded activation of the right ventricle. (2) *Right ventricular complex:* The initial activation was in the right ventricle and clearly preceded activation of the left ventricle. (3) *Ventricular fusion complex:* The initial activation was detected simultaneously in both the right and left ventricles.

Results

Ventricular rhythm disorders occurred in 26 of the 32 animals, the ectopic activity ranging from mild (fewer than 10 ventricular premature complexes/min) in 5 dogs to severe (multiple ventricular premature complexes and ventricular tachycardia) in 21 dogs. Ventricular fibrillation developed in 14 animals. Six dogs manifested no ventricular arrhythmias.

Identification of the stimulation site: The earliest inscription of the electrograms could identify the site of ventricular excitation during ventricular pacing (Fig. 2). As a result of right ventricular stimulation, early activation of the right ventricle preceded the earliest left

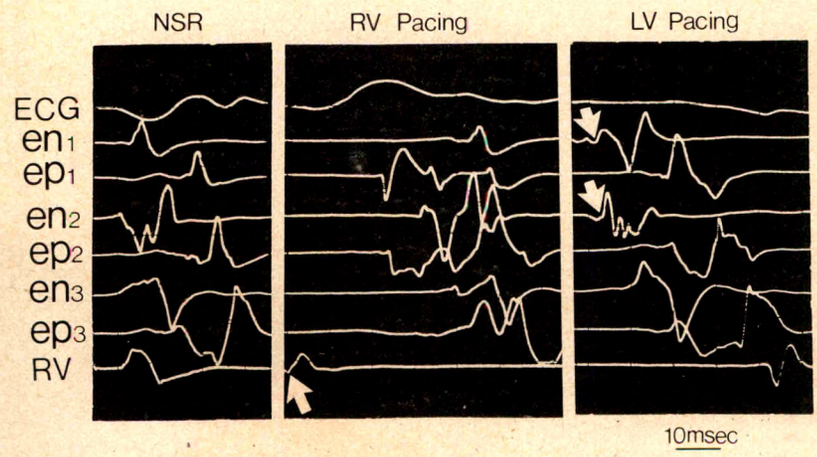


FIGURE 2. Polaroid® photograph of three ventricular complexes in a dog before coronary arterial ligation. During normal sinus rhythm (NSR), the sequence of activation is as expected: The endocardial electrograms preceded the corresponding epicardial electrogram. Right ventricular pacing **(center panel)** results in early right ventricular activation (RV, **arrow**) preceding the earliest left ventricular activation. The reverse is observed during left ventricular pacing **(right panel).** The left ventricular electrogram (en_1 and en_2, **arrows**) precedes the right ventricular electrogram. ECG = lead II of the electrocardiogram; en = endocardial; ep = epicardial; LV pacing = during pacing of the left ventricle, endocardial surface close to the central groups of electrodes depicted in Figure 1; RV pacing = during pacing of the right ventricle endocardial surface; 1, 2 and 3 = expected ischemic border and normal zones, respectively (Fig. 1).

ventricular electrogram by 20 msec. Similarly, left ventricular activation preceded right ventricular activation by 30 msec when the stimulation site was in the left ventricle. Hence, we could be reasonably certain that the earliest activation represented the initial exit point in the ventricles.

ABLE I

ncidence of Right (RV) Versus Left (LV) Ventricular ctopic Activity as Percent of Total Ectopic Activity*

Dog no.	Percent Ectopic Activity		Degree of Ventricular Arrhythmia†
	RV	LV	
1	33	67	Severe
2	35	65	Severe
6	0	100	Severe
8	20	80	Severe
9	13	87	Severe
11	21	79	Severe
15	27	73	Severe
17	33	67	Severe
18	47	53	Severe
19	38	62	Severe
20	27	73	Severe
21	37	63	Severe
22	65	35	Severe
24	24	76	Severe
28	65	35	Severe
29	0	100	Severe
31	21	79	Severe
32	70	30	Severe
3	0	100	Mild
7	19	81	Mild
12	100	0	Mild
14	0	100	Mild
23	0	100	Mild
25	0	100	Mild
26	0	100	Mild
27	0	100	Mild
30	0	100	Mild

* Excluding complexes with simultaneous premature activation of th ventricles.
† Mild = fewer than 10, severe = 10 or more ventricular premature mplexes/min.

Incidence of right and left ventricular premature activity after coronary arterial ligation: In the animals with only slight ectopic activity (fewer than 10 ventricular premature complexes/min, occurring for 3 to 5 minutes only), the ventricular premature complexes tended to arise from only one ventricle. In the animals with severe ventricular arrhythmia (multiple ventricular premature complexes and runs of ventricular tachycardia), multiple sites of initial activation in either or both ventricles were noted. Table I summarizes right and left ventricular premature activation in the individual dogs.

Electrophysiologic alterations leading to ectopic activity: Immediately after coronary arterial ligation there was marked delay, fragmentation and reduction in amplitude of the electrical activity in the central left ventricular epicardial ischemic zone. When the delay in the ischemic epicardium resulted in continuous activity beyond the T wave, ectopic ventricular complexes developed (Fig. 3). Both right and left ventricular premature complexes were associated with diastolic bridging of the electrical activity in the ischemic epicardial zone of the left ventricle. Thus, the right ventricular premature complex shown in panel A of Figure 3 and the left ventricular premature complex in panel B follow similar delayed activation of the ischemic epicardial zone of the left ventricle. Delayed and fragmented diastolic activity was never observed in the ischemic epicardial zone of the right ventricle (Fig. 4).

Premature activation during ventricular tachycardia: In the animals with severe ventricular arrhythmias, so-called right and left ventricular tachycardias were both evident (Fig. 4). Diastolic activity in the epicardial ischemic zone of the left ventricle was delayed in both types of ventricular tachycardia. However, in Figure 4 the exit points were in the right ventricle in complexes 1 and 2 and in the left ventricle in complexes 3 to 5. Occasionally a ventricular tachy-

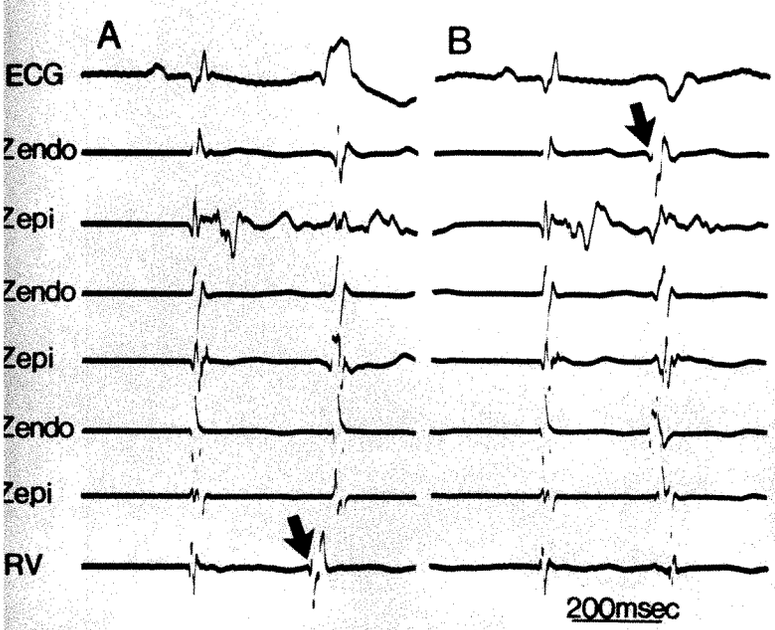


FIGURE 3. Lead II of the electrocardiogram (ECG) and seven composite electrograms in a dog 5 minutes after coronary arterial ligation. The composite electrode setting is explained in Figure 1. **Panel A,** a right ventricular premature complex follows the normal sinus complex with early activation in the right ventricular electrogram **(arrow). Panel B,** a left ventricular premature complex follows the normal sinus complex with early activation in the ischemic zone endocardial electrogram **(arrow).** Note that delay and fragmentation of the activation in the ischemic epicardial zone of the left ventricle (IZepi) follow the normal sinus complex and bridge it with the ventricular premature complex in both instances. This zone shows no diastolic activity before the normal sinus complex. endo = endocardial electrogram; epi = epicardial electrogram; IZ, BZ and NZ = ischemic, border and normal zones of the left ventricle, respectively; RV = composite right ventricular endocardial electrogram.

cardia terminated after a shift in the exit site from one ventricle to another. In ventricular complexes 1 to 4 of Figure 5, the exit site appears to be in the right ventricle. Ventricular complex 5 was initiated by early activation in the left ventricle, and the tachycardia terminated. It should again be emphasized that continuous delayed and fragmented activity in the left ventricular epicardial ischemic zone led to the varying right and left ventricular exit points.

The multiple exit points and their time relations may account for the appearance of ventricular fusion complexes. The site of initial activation for ventricular complex 2 in Figure 6 appeared to be in the left ventricle because right ventricular activation occurred 45 msec later. Ventricular complex 3 appeared to arise from almost simultaneous activation of the left and right ventricles. Ventricular complex 4 clearly began in the right ventricle. The degree of fusion and the preponderance

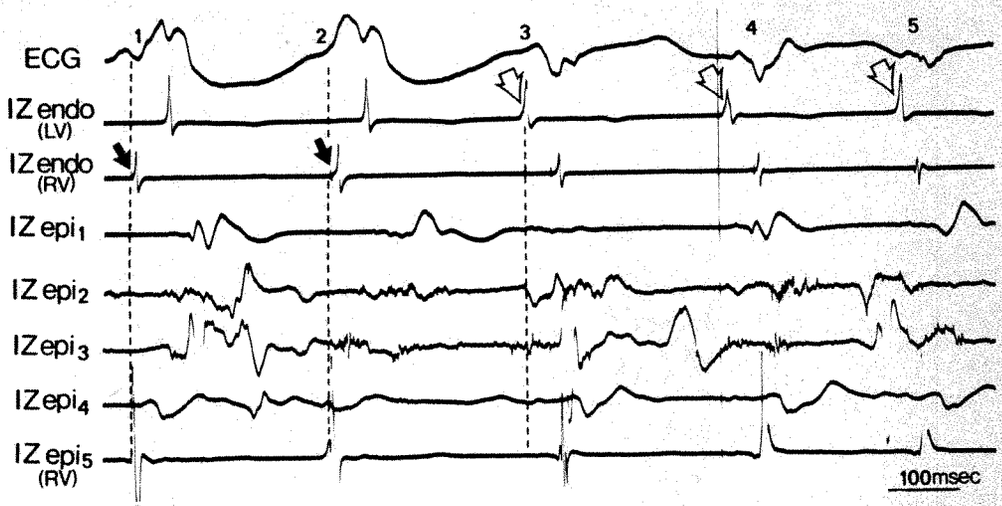


FIGURE 4. Lead II of the electrocardiogram (ECG) and seven electrograms from seven single bipolar electrodes in a dog 6 minutes after coronary arterial ligation. Note that complexes 1 and 2 are the terminal portion of a ventricular tachycardia originating in the right ventricle (RV). **Black arrows** point to early right ventricular endocardial activation preceding left ventricular endocardial activation by 50 msec. The ventricular tachycardia changes configuration abruptly in complexes 3 to 5 as the earliest activation shifts suddenly from the right to the left ventricle. Subsequently, left precedes right ventricular endocardial activation by 50 msec **(white arrows).** Delayed and fragmented activity in the ischemic zone ($IZepi_1$ through $IZepi_4$) in the left ventricle bridges the diastolic interval in both the right and left ventricular complexes. endo = endocardial surface; epi_1 through epi_4 = recording from four epicardial sites in the left ventricle; epi_5 = recording from epicardial site in the ischemic zone of the right ventricle close to the septum; IZ = ischemic zone; LV = left ventricle (center of the ischemic zone).

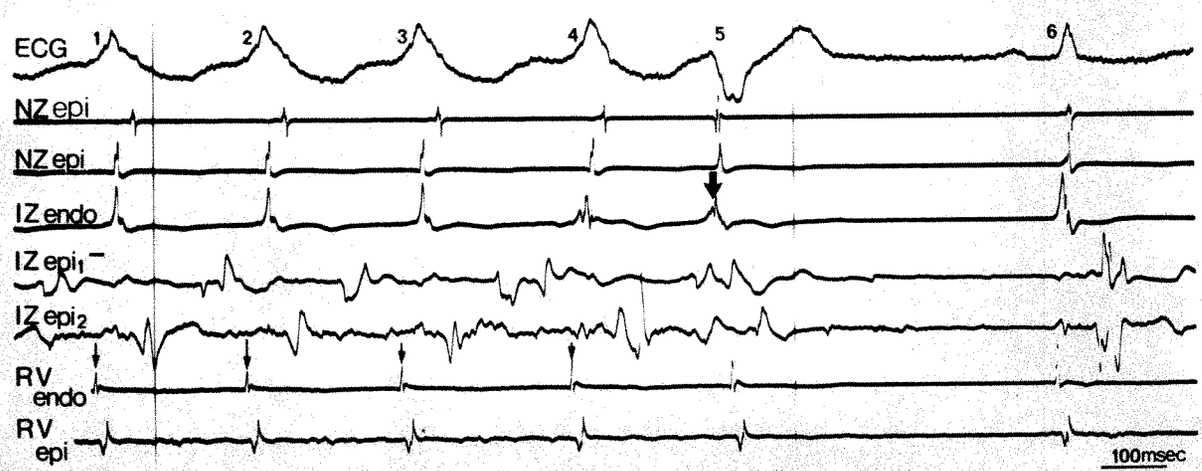


FIGURE 5. Lead II of the electrocardiogram (ECG) and seven single bipolar electrograms in a dog 6.5 minutes after coronary arterial ligation. Note the sustained ventricular tachycardia in complexes 1 to 4. The earliest activation (outside the ischemic zone epicardium [IZepi]) in these complexes is in the right ventricular endocardial electrogram **(small arrows)**. Delayed and fragmented epicardial activity in the ischemic zone of the left ventricle bridges the diastolic interval between right ventricular ectopic complexes. The exit site of the ventricular tachycardia shifts suddenly in complex 5. The earliest subsequent activation is in the endocardial surface of the ischemic zone in the left ventricle **(large arrow).** The activation sequence in the ischemic zone (IZepi 1 and 2) changes; as a result, no diastolic bridging activity occurs and the ventricular tachycardia terminates. endo = endocardial surface; epi_1 and epi_2 = two epicardial recording sites from the center of the ischemic zone; IZ = ischemic zone; NZepi = normal zone electrograms from two points adjacent to the ischemic zone; RV = right ventricle.

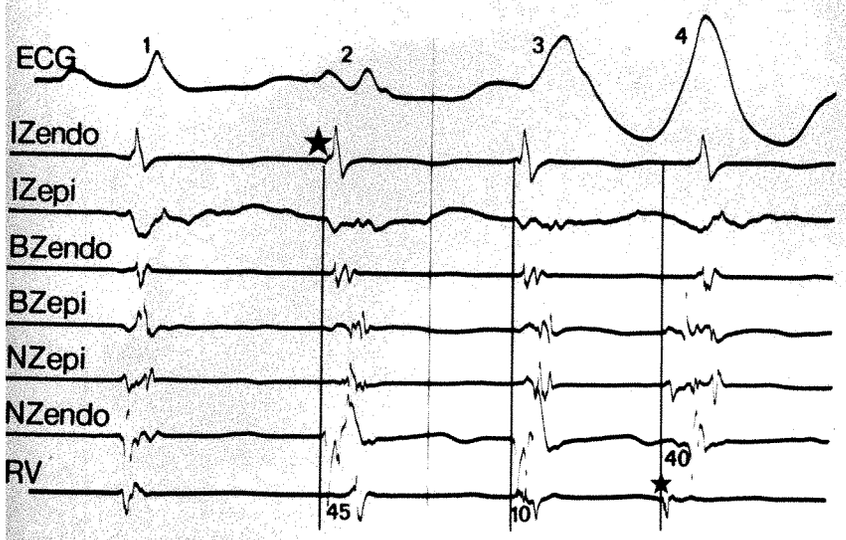
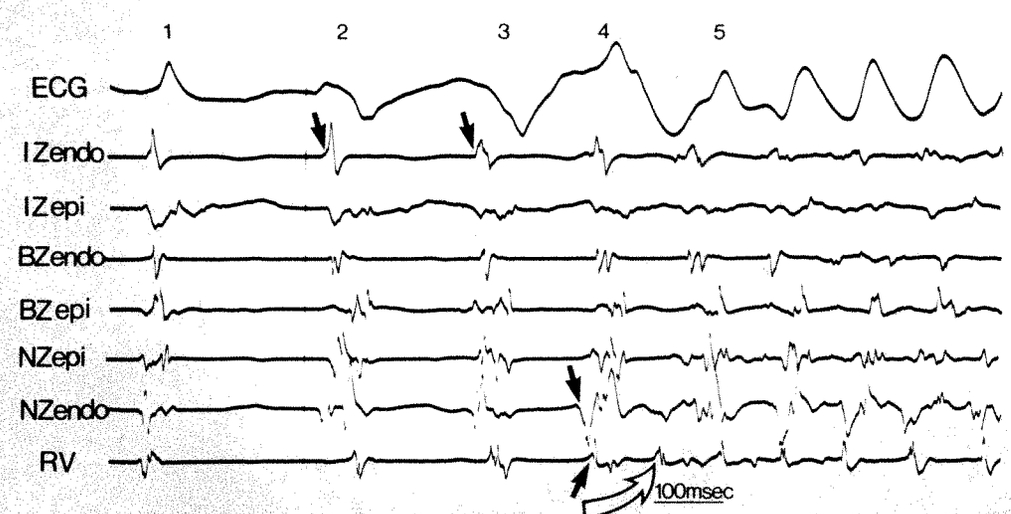


FIGURE 6. Lead II of the electrocardiogram (ECG) and seven composite electrograms in a dog 3.5 minutes after coronary arterial ligation. The electrodes are positioned as in Figure 1 except that the normal and border zone epicardial electrogram (NZepi and BZepi) include electrodes positioned in the normal and border zones in the right ventricle. Before complex 1, there is no electrical activity in the left ventricular ischemic zone (IZepi). Continuous delayed and fragmented activity is not observed. However, after complex 1 the ischemic zone (IZepi) activation becomes markedly fragmented, resulting in an ectopic ventricular complex indicated at 2. Ventricular endocardial activation in the left ventricle (**star** in IZendo) precedes the right ventricle by 45 msec, and complex 2 is a left ventricular complex. As diastolic bridging activity continues in IZepi, ectopic complexes 2 and 3 occur. Complex 3 has an almost simultaneous early activation in both the right and left ventricular endocardial surfaces and therefore is a ventricular fusion beat exiting in both ventricles. The right ventricular endocardium precedes the left by 40 msec (**star** in RV) in complex 4, which is a right ventricular complex. Abbreviations as in Figure 3.

of activation of one ventricle over the other could vary depending on the time relations of the independent exit sites. Multiple endocardial exit points were noted shortly before the rhythm disorder deteriorated into ventricular fibrillation (Fig. 7). The time relation between right and left ventricular activation changed with each complex (beats 2 to 5, Fig. 7). There were both right and left ventricular exit points and variable exits in the left ventricle, as indicated by the different configurations observed in the recorded electrograms in animals with ventricular tachycardia or ventricular fibrillation.

Discussion

Right ventricular arrhythmias resulting from left ventricular ischemia or infarction: This study suggests that ventricular arrhythmias after acute coronary occlusion in the experimental animal may arise from both the right and left ventricles. When ventricular ectopic activity was rare, the arrhythmias were more uniform and usually confined to one ventricle. In contrast, more severe rhythm disturbances were associated with multiple exit sites and occurred more frequently in the left ventricle than in the right. Right ventricular



IGURE 7. Lead II of the electrocardiogram (ECG) and seven composite electrograms 7 minutes after coronary arterial ligation in the same dog as Figure 6. The electrode setting is as in Figure 1 and the abbreviations are as in Figure 3. After complex 1, which is of sinus origin, a short rapid ventricular tachycardia deteriorates into ventricular fibrillation. Complex 2 is a left ventricular complex. Right ventricular activity occurs 45 msec ter the initial left ventricular endocardial activation. Complex 3 is again a left ventricular complex. However, the exit point is different, as indicated the different configurations in the electrograms and the electrocardiogram. In complex 4 the right ventricular activation (**arrow** in RV) is very ose to the left ventricular activation (**arrow** in IZendo), suggesting an independent exit in the right ventricle producing a ventricular fusion beat. complex 5 activity in the right ventricle (**white arrow** in RV) occurs before that in all other areas of the heart, after which the electrical activity the heart becomes completely disorganized, resulting in ventricular fibrillation.

arrhythmias have been reported in the presence of acute myocardial infarction.[18] In the presence of an anteroseptal myocardial infarction (produced in the model used in our experiments), the right ventricular muscle adjacent to the septum is slightly but definitely involved. We analyzed the acute electrophysiologic disturbances leading to the development of so-called right and left ventricular ectopic activity and believe that ischemic involvement of the right ventricular free wall is not sufficient to explain right ventricular arrhythmias. Our studies and others[20–25] have demonstrated that specific delay and fragmentation of the normal impulse in the ischemic epicardial zone of the left ventricle are associated with ventricular arrhythmias after acute coronary occlusion. Furthermore, in this study the type and location of the characteristic epicardial delayed and fragmented activity resulting in ventricular ectopic activity and ventricular fibrillation were similar for arrhythmias that originated in the right and left ventricles.

Delayed and fragmented activity was never observed over the epicardium of the ischemic right ventricle. Hence, the initiation of a so-called right or left ventricular premature complex depended on the specific efferent pathways of the reentry cycle from the left ventricular ischemic zone demonstrating epicardial diastolic bridging. In a previous study[25] we reported that left ventricular arrhythmias originating in the endocardial ischemic zone of the left ventricle are produced from delayed and fragmented activity in the overlying ischemic epicardium, spreading to the endocardial surface. Premature activation of the left ventricular ischemic endocardium always followed the initiation of the right ventricular ectopic complexes; hence, conduction pathways leading directly from the left ventricular ischemic epicardium to the right ventricular endocardium could be postulated. Direct transmission by way of the epicardial layers from the left to the right ventricle could be suggested. However, we never observed epicardial spread from the ischemic zone to the remainder of the heart.[25] Furthermore, the epicardium of the right ventricle overlying the ischemic zone did not appear to sustain delayed and fragmented activation bridging diastole.

Mechanism of right ventricular arrhythmias—bridging activity: The reasons for these findings are unclear. Possibly the relatively thin right ventricular wall with an extensive Purkinje network precluded any major conduction delay or fragmentation. A more plausible mechanism may involve the anterior and ischemic portions of the thick interventicular septum. The bridging activity during ventricular arrhythmia was always documented in the subepicardial muscle layers that did not contain Purkinje fibers, and the ischemic endocardial activation remained synchronized and nonfragmented.[20–24] Similar layers of ventricular muscle are also present in the right side of the interventricular septum. Any extension of diastolic bridging activity into the right side of the interventricular septum could easily excite the overlying right ventricular Purkinje network and produce right ventricular premature beats.

Role of multiple exit sites: The efferent reentrant pathway was not necessarily confined to a single exit site. Multiple simultaneous activations into both the right and left ventricles were demonstrated clearly in our experiments. A shift in the efferent pathway could be associated with the termination of a stable reentrant tachycardia. The sudden change in the reentry cycle appeared to cancel the previous stable circus movement in the same way that an ectopic beat (for example, pacemaker-induced) could terminate ventricular tachycardia.[26] However, multiple exit points may have a deleterious effect on the normal portion of the heart because multifocal excitations could arrive asynchronously in the normal myocardium and produce ventricular fibrillation (Fig. 7).

Clinical implications: Our experimental study supports previous clinical observations indicating that ventricular premature complexes and ventricular tachycardia originating in the right ventricle may be the result of myocardial injury. In a review[16] of ventricular tachycardia in patients with a left ventricular aneurysm it was noted that a significant number of patients had typical right ventricular tachycardia. Bodenheimer et al.[17] showed that patients with coronary artery disease may have both right and left ventricular premature complexes. Another study[3] demonstrated that right and left ventricular premature complexes were associated with a similar increase in the risk of sudden death. However, because there is no single cause of ventricular premature activity, these observations do not contradict other reports[12–16,27] indicating that right ventricular arrhythmias occur mainly in young healthy persons.

We have demonstrated that acute injury to the anteroseptal region of the heart resulted in arrhythmias exiting in both ventricles. These arrhythmias appeared to arise more frequently from the left than from the right ventricle, a finding that may account for the predominance of left ventricular arrhythmias observed in patients with heart disease.[12–16,27] It also appears that more extensive injury to the left ventricle provides for more numerous potential subendocardial exit points to the remainder of the heart. The ultimate origin of ventricular ectopic activity and the site or sites of exit (and thus the electrocardiographic configuration) can differ. The apparent site of origin of ventricular arrhythmias should not be the sole determinant of the benign or malignant properties of the arrhythmia.

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Effect of Stenotic Dimensions and Blood Flow on the Hemodynamic Significance of Model Coronary Arterial Stenoses

KIRK LIPSCOMB, MD, FACC
STEVEN HOOTEN, BA

Dallas, Texas

The effect of length, diameter and exit angle of a stenosis, percent stenosis, blood flow through the stenosis and blood viscosity on the hemodynamic significance of model coronary arterial stenoses was studied. The hemodynamic significance was quantitated by the pressure gradient across the stenosis. The total pressure gradient is the sum of the gradient due to nonturbulent flow through the body of the stenosis and the gradient due to turbulent flow at the exit from the stenosis. The gradient due to turbulent exit flow is the result of the loss of the kinetic energy possessed by the high velocity intrastenotic flow and is predicted by the Bernoulli equation. The gradient due to turbulent exit flow is proportional to the product of flow^2 and diameter of the stenosis^{-4}. The length of a stenosis has a small effect on the gradient due to turbulent flow because the kinetic energy possessed by the intrastenotic flow partly depends on the development of the flow profile, which in turn depends on length of the stenosis. The gradient is not affected by varying the stenosis exit angle from 10° to 90°. The pressure gradient due to nonturbulent intrastenotic flow is predicted from the Poiseuille equation and is therefore proportional to the product of blood viscosity, length of the stenosis, blood flow and diameter of the stenosis^{-4}. Because the pressure gradient due to turbulent flow is proportional to the square of flow whereas the gradient due to nonturbulent flow is linearly proportional to flow, the gradient due to turbulent flow/gradient due to nonturbulent flow ratio increases as flow increases. Because changes in length of the stenosis, blood viscosity and flow affect the turbulent and nonturbulent components of the pressure gradient to different degrees, the relative significance of a change in one of these values depends on the flow rate. Percent stenosis can be used to estimate the component of pressure gradient due to turbulent exit flow, but only if the flow velocity in the nonstenotic portion of the vessel is known. On the basis of these results, the hemodynamic significance of a coronary stenosis can be estimated using documented, theoretically sound concepts.

The hemodynamic significance of a coronary arterial stenosis must frequently be assessed from an angiogram of the vessel containing the stenosis. The angiographer uses the variables of diameter and length of the stenosis, percent stenosis and estimated blood flow through the stenosis to decide whether the stenosis is significant. However, the contribution of each of these variables to the significance of a stenosis is unclear. In this study we attempted to determine the relation among the dimensions, flow and hemodynamic significance of a stenosis by studying the flow of blood through model stenoses. Although the stenoses found in atherosclerotic arteries do not always conform to the relatively simple configurations of a model, we believe that an understanding of the principles underlying the determination of the significance of a stenosis of simple configuration is prerequisite to understanding stenoses with more complicated configurations.

From the Cardiovascular Section, Medical Service, Veterans Administration Hospital, Dallas, Texas, and the Department of Internal Medicine, University of Texas Health Science Center, Southwestern Medical School, Dallas, Texas. This work was supported in part by a grant from the Ischemic Heart Disease SCOR, National Institutes of Health, Bethesda, Maryland. Manuscript received March 23, 1978; revised manuscript received June 13, 1978, accepted June 14, 1978.

Address for reprints: Kirk Lipscomb, MD, Cardiovascular Section, Veterans Administration Hospital, 4500 South Lancaster Road, Dallas, Texas 75216.

A coronary arterial stenosis alters coronary hemodynamics by creating a pressure gradient between the aorta and the coronary artery distal to the stenosis. This decreased distal pressure then results in either a decrease in flow or a compensatory decrease in arteriolar resistance. Although either direct or indirect measurements of coronary flow can be used to assess the significance of a stenosis, these measurements are relatively nonspecific because the flow is dependent on arteriolar resistance as well as the pressure gradient created by the stenosis. Therefore, in this study we used the pressure gradient as a specific measure of significance of stenosis.

Determinants of Pressure and Flow Across a Stenosis

Visual and pressure-flow studies have indicated that flow through a stenosis is nonturbulent through the body of the stenosis but becomes turbulent at the exit of the stenosis.[1,2] Therefore, the total pressure gradient should equal the sum of the gradients caused by the nonturbulent intrastenotic flow and the turbulent exit flow.[1,3,4] Because the variables that determine the pressure gradient relate differently to the nonturbulent and turbulent flow, the first step in studying these variables is to assess from the total pressure gradient the portion due to each type of flow. This assessment is possible because the pressure gradient due to nonturbulent flow is linearly proportional to the flow rate, whereas the gradient due to turbulent flow is proportional to the square of the flow rate.[5] After multiple pressure gradient-flow points are measured for a given stenosis, these points are mathematically fitted to the equation:

$$PG = t\,F^2 + n\,F \qquad (1)$$

where PG = total pressure gradient in mm Hg and F = flow in ml/min. After determining the coefficients in equation 1, it is assumed that:

$$PG_t = t\,F^2 \qquad (2)$$

$$PG_n = n\,F \qquad (3)$$

where PG_t = pressure gradient due to turbulent flow in mm Hg and PG_n = pressure gradient due to nonturbulent flow in mm Hg.

According to equation 2 the coefficient t incorporates those factors that, in addition to rate of flow, affect the pressure gradient due to turbulent flow. Likewise, according to equation 3 the coefficient n incorporates those factors that, in addition to rate of flow, affect the gradient due to nonturbulent flow.

Turbulent flow: *The component of the pressure gradient due to turbulent flow* occurs when the high velocity flow within the stenosis meets the slow velocity flow downstream.[6] Turbulence is thereby created, and the kinetic energy present in the high velocity stream is dissipated as heat. Bernoulli's theorem states that the total energy possessed by a fluid is the sum of the static energy (pressure) and the kinetic energy.[5,7] The kinetic energy possessed by a fluid is proportional to the product of its density and the square of its velocity. At normal values for coronary vessel diameter and flow rate, the velocity is low enough to permit the kinetic energy to be disregarded. However, when the velocity increases to pass through the decreased cross-sectional area of a stenosis, pressure is converted to kinetic energy. If the velocity profile is flat—that is, the velocity of the fluid is identical at the periphery and the center of the flow stream—the velocity is equal to volume of flow divided by cross-sectional area. However, as viscous fluids pass down a tube, they change from a flat profile to a profile in which the center of the flow stream has higher velocity than the periphery.[5,7] When this profile is fully developed, as in laminar flow, the velocity at the center is twice the average velocity. As a result, twice as much total pressure is converted to kinetic energy than if the flow profile were flat. The coefficient α is used to correct for this increase in kinetic energy over that calculated assuming a flat profile.[5,6] Flow with a flat profile has an α value of 1.0, and fully developed laminar flow has an α value of 2.0. As the fluid passes through the exit of the stenosis, the velocity of the fluid decreases. At this point the kinetic energy possessed by the high velocity flow within the stenosis may theoretically be totally recovered and converted back to pressure or totally or partially dissipated in turbulence.[5,6] The coefficient s is used to quantitate the relative amount of kinetic energy dissipated. This coefficient ranges from 0, which indicates no dissipation, to 1.0, which indicates a dissipation of all of the kinetic energy possessed by the intrastenotic flow.

A frequently used formula for determining the relative amount of kinetic energy dissipated was originally theoretically developed to determine the energy loss at a sudden expansion in a pipeline.[5] This formula uses the equivalent of an s value equal to:

$$[(0.02 \times \%\ \text{stenosis}) - (0.0001 \times \%\ \text{stenosis}^2)]^2$$

where, % stenosis = [(diameter of nonstenotic lumen − diameter of stenotic lumen)/diameter of nonstenotic lumen] × 100. However the actual value of s under a given set of conditions must be determined experimentally. Summarizing mathematically:

$$PG_t = \frac{KE}{1332} \times s$$

$$KE = 1/2\,\rho\alpha V^2$$

$$V = \frac{F}{CSA} \times \frac{1}{60}$$

$$CSA = \pi\left(\frac{D}{2} \times \frac{1}{10}\right)^2$$

Combining and rearranging:

$$PG_t = K_t\,\rho\alpha s\,D^{-4}\,F^2 \qquad (4)$$

where, α = kinetic energy correction factor; CSA = cross-sectional area in cm^2; D = diameter in mm; F = flow in ml/min; K_t = coefficient combining all constants; KE = kinetic energy in $dyne/cm^2$; PG_t = pressure gradient due to turbulent flow; ρ = density; s = coefficient quantitating relative amount of intrastenotic kinetic energy dissipated in turbulence; and V = average velocity in cm/sec.

The basic kinetic energy equation is usually given in units of the centimeter-gram-second system. The coefficient K_t in equation 4 combines all constants including those to convert to the units used in this study. The theoretical K_t in equation 4 equals 0.0017. Combining equations 2 and 4 yields:

$$t = K_t\,\rho\,\alpha\,s\,D^{-4} \qquad (5)$$

Nonturbulent flow: *If one assumes that flow is laminar within the stenosis, the component of the pressure gradient due to nonturbulent flow should be predicted by Poiseuille's equation.*[7] Thus the pressure gradient due to nonturbulent flow should be directly proportional to blood flow and viscosity and length of stenosis, and inversely proportional to the fourth power of the diameter. Poiseuille's equation is usually given in the centimeter-gram-second system:

$$pg_n = \left(\frac{8}{\pi}\right)\mu\,l\,r^{-4}\,f$$

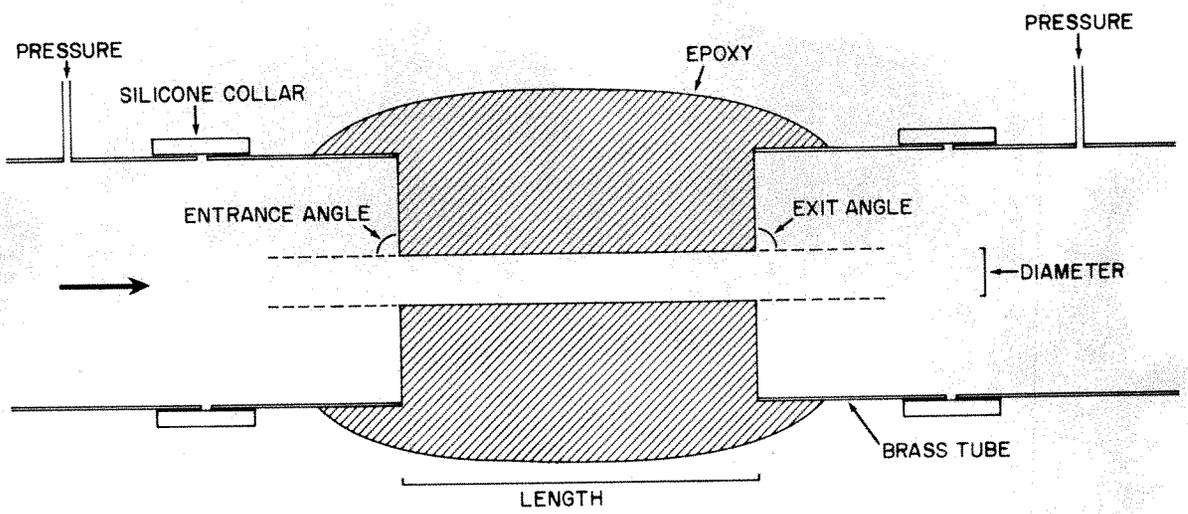


FIGURE 1. Diagram of model stenosis showing anatomic details.

Converting to units used in this study and combining constants:

$$PG_n = K_n \mu L D^{-4} F \quad (6)$$

where, D = diameter in mm; f = flow in ml/sec; F = flow in ml/min; K_n = coefficient combining all constants; l = length in cm; L = length in mm; pg_n = pressure gradient due to nonturbulent flow in dynes/cm^2; PG_n = pressure gradient due to nonturbulent flow in mm Hg; r = radius in cm; μ = viscosity in poise. The theoretical K_n in equation 6 equals 0.510. Combining equations 3 and 6 yields:

$$n = K_n \mu L D^{-4} \quad (7)$$

Using these concepts we have studied the pressure gradient caused by the flow of blood through stenoses. The effect of the anatomy of the stenosis was determined by using model stenoses of precise dimensions, and the effect of blood viscosity was determined by comparison with water. The results are highly consistent with the predicted results based on the foregoing hypotheses.

Methods

Model stenoses: These were made from brass tubing and epoxy resin (Hysol C8 4143) molded over brass rods of known diameter. A diagram of the stenosis is shown in Figure 1. A silicone elastomer collar connected the brass tubing which was part of the stenosis to the brass tubing connected to the perfusion line. Proximal and distal pressures were measured through 22 gauge cannulas soldered perpendicularly to the perfusion lumen.

All stenoses were molded in duplicate. Several groups of stenoses were molded, with a different anatomic aspect of the stenosis altered in each group. In the first group the length and diameter of the stenosis were altered while the entrance and exit angles were held constant at 90°, and the diameters of the proximal and distal lumen were held constant at 3.2 mm. Five diameters—0.50, 0.80, 1.14, 1.64 and 2.36 mm—were molded in stenoses of five lengths—1, 2, 5, 10 and 20 mm. In the second group exit angles were altered whereas length of the stenosis was held constant at 5 mm, diameter was held constant at either 0.80 or 1.14 mm and the diameters of the proximal and distal lumen were held constant at 3.2 mm. In this group the angle at one end of the stenosis was 90° and the angle at the other end was either 90° or 10°. By reversing direction of flow in the stenoses with different angles, the exit angle was altered from 90° to 10° in the same stenosis. In the third group, proximal and distal lumen diameters were altered while length of the stenosis was held constant at 5 mm, diameter was held constant at either 0.80 mm or 1.64 mm, and entrance and exit angles were held constant at 90°. The diameters of the proximal and distal lumens were either 2.4 or 4.0 mm.

Stenosis perfusion: The stenoses were perfused with water and with blood. Water temperature was 20° C. Water pressure was maintained by gravity. Three week old citrate-anticoagulated human blood was used after the hematocrit was adjusted to 40 percent by adding packed cells or withdrawing plasma. Blood pressure was maintained by enclosing the blood in a plastic bag that was placed in a rigid container next to a pressurized air bag. Both water and blood pressure, as measured with the cannula just proximal to the stenosis, was held between 80 and 110 mm Hg. At the distal end of the perfusion system blood drained into another plastic bag. Thus the blood had minimal contact with air. The blood was maintained at 37° C with use of an agitating water bath. The hematocrit of the perfused blood was periodically checked to be certain that agitation was sufficient to keep the cells and plasma mixed. During a pressure gradient-flow determination, blood or water flowed through a blood filter, through the flow transducer, past the proximal pressure cannula, through the stenosis, past the distal pressure cannula and finally through a variable constrictor.

Measurements: All measurements were recorded on a physiologic recorder (Electronics for Medicine) at a paper speed of 25 mm/sec. Pressure was measured through well flushed, matched transducers (Biotech BT-70). The gradient was determined with electronic subtraction. The pressure cannulas were positioned 1 cm proximal and distal to the stenoses. Because of the possibility that the distance between the end of the stenosis and the distal pressure cannula may have affected the distal pressure measurement, several stenoses were tested with this distance set at both 1 and 2 cm. This distance was found not to affect the distal pressure. Blood flow was measured with an ultrasonic flowmeter (model 1012, L & M Electronics, Daly City, California) at a carrier frequency of 8.6 megahertz. The system was calibrated in our laboratory by timed collections of blood. The output was filtered at 5 hertz. Water flow was measured by timed collections.

A single determination of stenotic hemodynamics was performed by perfusing blood or water through a stenosis at

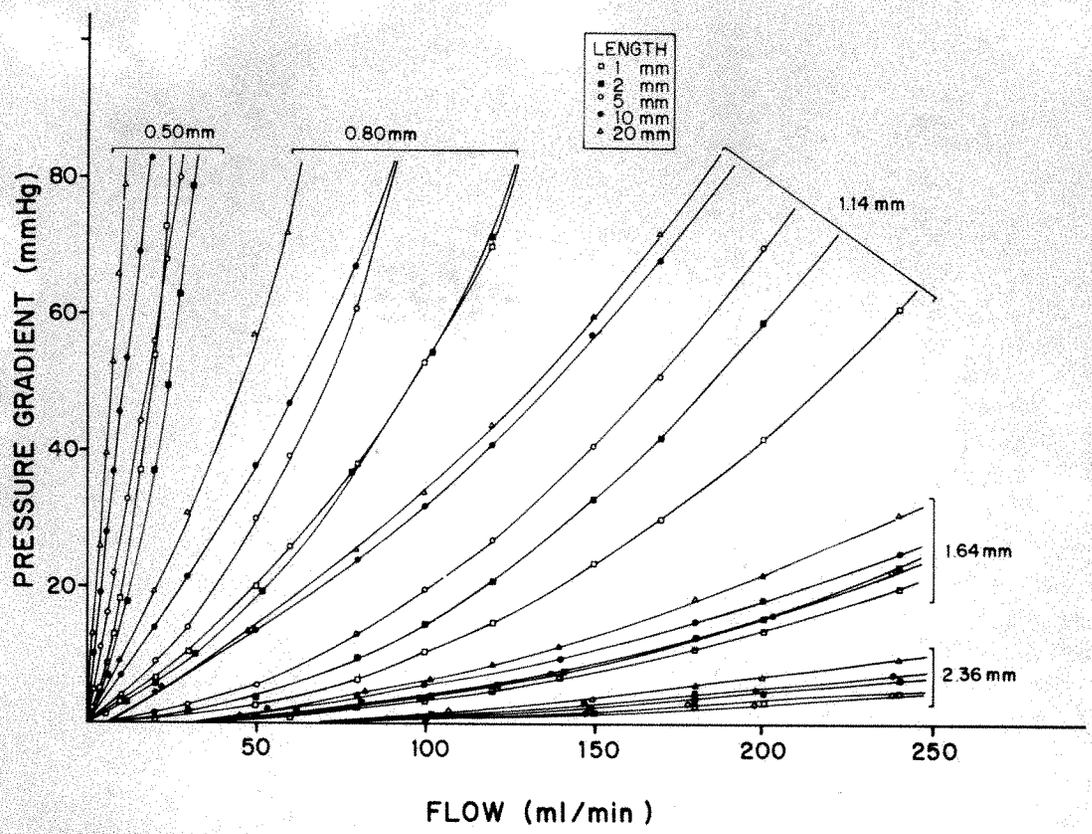


FIGURE 2. Relation of pressure gradient to blood flow for each diameter and length of stenosis. Each curve is the best fit of the measured pressure gradient-flow values to the equation $PG = tF^2 + nF$ (Equation 1 in text). The diameters of the stenoses are shown by the brackets.

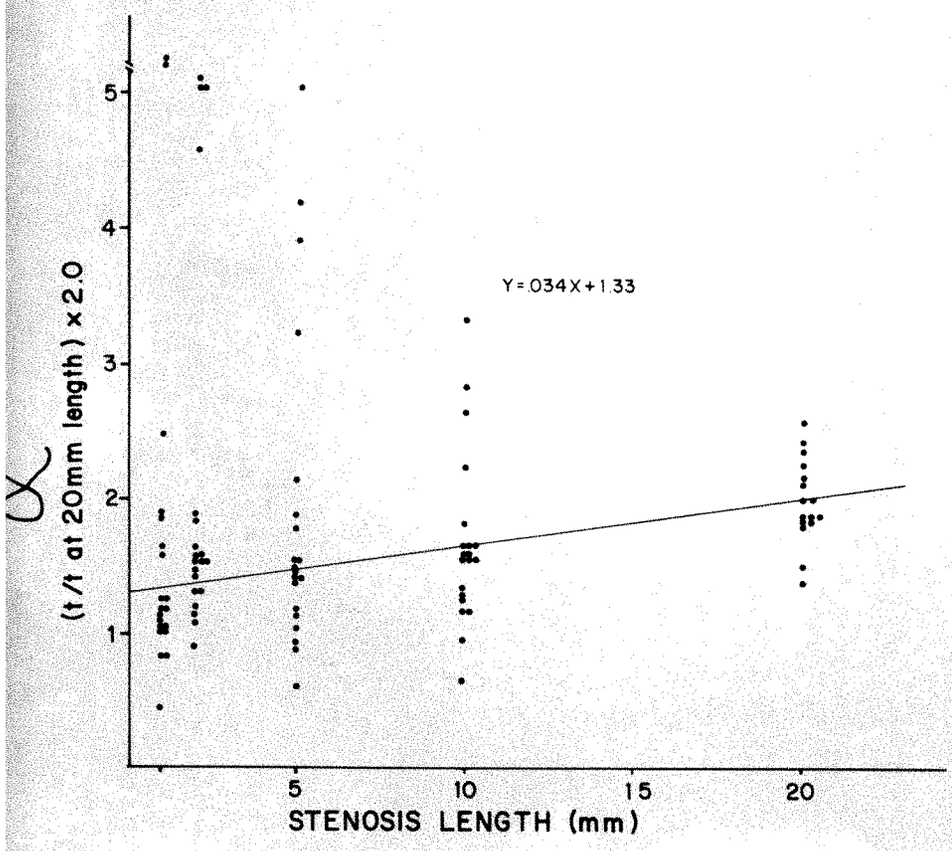


FIGURE 3. Relation of α to length of stenosis. The α coefficient corrects for the amount of kinetic energy present in the high velocity intrastenotic flow relative to the kinetic energy calculated assuming a flat velocity profile. α was assumed to be maximum (2.0) at lengths of 20 mm and was determined by dividing the t of each stenosis by the average t of the 20 mm long stenoses of the same diameter. Values of α above 4.0 were disregarded as spuriously high.

8 to 12 different flow rates. At each flow rate the pressure gradient was measured. Pressure gradient-flow measurements were spaced between 0 and the lesser of either a pressure gradient of 80 mm Hg or a flow rate of 250 ml/min. Each stenotic configuration was molded in duplicate and each stenosis was studied with flow in each direction, thereby giving four separate determinations for each configuration. Each of the four determinations was treated separately in the analysis of the results except in Figure 2, where all the points from the four determinations in the same configuration of stenosis were combined. In stenoses that were 1 and 2 mm long with a diameter of 1.12 mm, those that were 1, 2 and 5 mm long with a diameter of 1.64 mm, and all of those with a diameter of 2.36 mm, the component of the pressure gradient due to nonturbulent flow was so small it was assumed to be 0. Similarly, in the 20 mm long stenosis with a diameter of 0.5 mm, the component of the gradient due to turbulent flow was assumed to be 0.

The results were statistically analyzed with the aid of a computer (DEC-10) and a programmable calculator (Texas Instruments SR-52). All regression equations were determined using the method of least squares. Where appropriate, the regression equation was forced to pass through 0.[8] The t and n coefficients in equation 1 were determined by the method

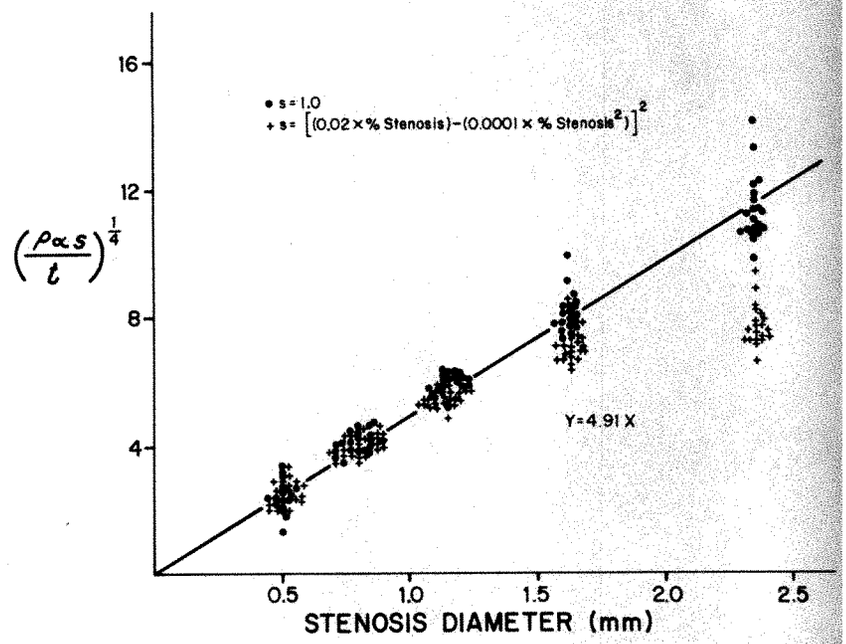


FIGURE 4. Relation of the diameter of the stenosis to the t coefficient modified by ρ, α and s. The diameter of the nonstenotic lumen is 3.2 mm. Separate results were plotted for two s values: (1) $s = [(0.02 \times \%$ stenosis$) - (0.0001 \times \%$ stenosis$^2)]^2$, and (2) $s = 1.0$. The regression equation is $(\rho \alpha s/t)^{1/4} = (1/K_t)^{1/4} D$, which is derived from equation 5 in the text. The relation is linear when $s = 1.0$, indicating that this is the proper value for s. The regression coefficient $(1/K_t)^{1/4}$ is 4.91, from which K_t is calculated to be 0.0017, the same as the theoretically derived K_t. See equations 4 and 5 for abbreviations.

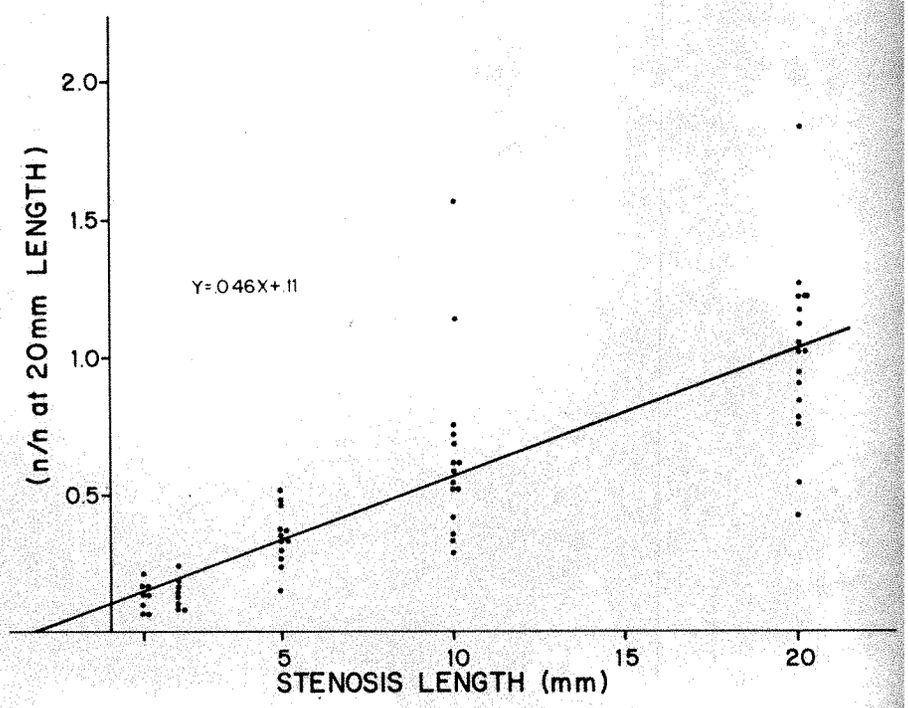


FIGURE 5. Relation of n (nonturbulent flow coefficient) to length of stenosis. The coefficient n was normalized in each stenosis by dividing n by the average n of the 20 mm long stenoses of the same diameter. As expected from equation 7, n is proportional to length. However, the length axis intercept is at −2.3 mm. This additional length is empirically termed "inlet length."

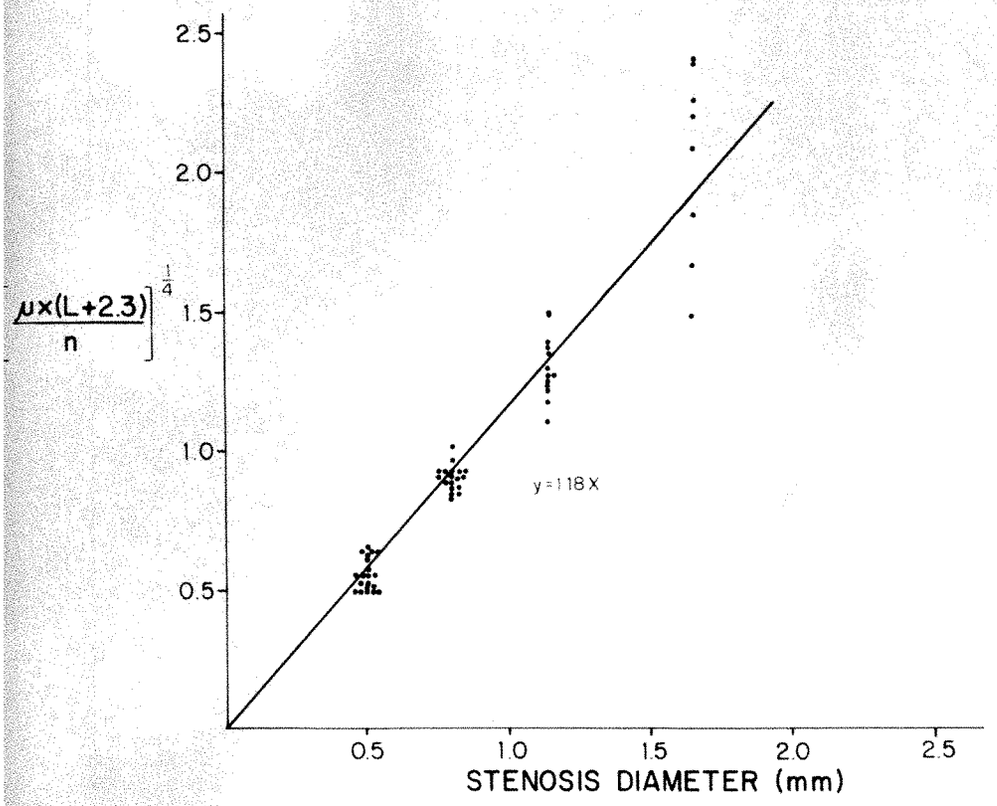


FIGURE 6. Relation of the diameter of the stenosis to the *n* coefficient modified by length and viscosity. The regression equation is $(\mu (L + 2.3)/n)^{1/4} = (1/K_n)^{1/4} D$, which is derived from equation 7 in the text. The value of viscosity used was 0.025. The regression coefficient $(1/K_n)^{1/4}$ is 1.18, from which K_n is calculated to be 0.52. The theoretically derived K_n is 0.51.

in which the least squares is determined by normal equations.[9]

Results

Total pressure gradient: The relation of total pressure gradient to blood flow for each length and diameter of stenosis is shown in Figure 2. Each curve is the best fit of the pooled pressure gradient-flow measurements from the four separate determinations made for each size of stenosis. The average standard error of estimate for these curves is 4.2 mm Hg. The nonlinearity of the relation is apparent. The graph illustrates that in the flow range studied, which is approximately that found in the in vivo coronary circulation, stenoses become significant as their luminal diameter decreases to approximately 1.5 mm. The graph also illustrates the significantly greater effect a relative change in diameter has on the pressure gradient compared with a change in length.

For each of the four stenoses of each diameter and length, the points relating pressure gradient and flow were then mathematically fitted to equation 1. In this way the pressure gradient due to the turbulent exit flow and the gradient due to the nonturbulent intrastenotic flow could be separated and studied independently. The average standard error of estimate for these curves was only 2.8 mm Hg. However the relative distribution of pressure gradient between tF^2 and nF in equation 1 was quite sensitive to small random variation in the pressure gradient-flow measurements. Most of the scatter in Figures 3 to 6 is the result of this problem with the mathematical separation process.

Pressure gradient due to turbulent exit flow: The component of pressure gradient due to turbulent exit flow is represented by tF^2 in equation 1. According to equation 5, t should be equal to $K_t \rho \alpha s D^{-4}$. The density (ρ) of blood was assumed to be 1.06.[10] The relation of α, s and diameter of stenosis (D) to t were then tested.

The α coefficient is the correction factor for the amount of kinetic energy present over that predicted assuming a flat velocity profile. It theoretically ranges from 1.0 for a flat profile to 2.0 for a fully developed profile. Because it depends on the development of the profile, and this development in turn depends on length, it should be dependent on length of the stenosis. This dependence was tested by comparing the t coefficients for blood when only length was varied. If the flow profile at the exit of the 20 mm long stenoses was assumed to be fully developed and therefore represented by an α value of 2.0, the extent of the development of the flow profile for each stenosis could be determined by the formula:

$$\alpha = (t/\text{average } t \text{ of 20 mm long stenoses of same diameter}) \times 2.0.$$

In Figure 3, α is plotted against length for each stenosis. There is a small but definite influence of length (L) on the development of the flow profile, represented mathematically as:

$$\alpha = 0.034\ L + 1.33 \quad (8)$$

Obviously this relation holds only for lengths of less than 20 mm. Lengths greater than 20 mm are assumed to have a constant α value of 2.0.

The proper value of s *and the relation of diameter of the stenosis to* t *were then determined.* In each stenosis the diameter was compared with the value of t, modified by the density, $\propto$ calculated from equation 8 and s. To show this relation, equation 5 is rearranged to the regression equation:

$$\left(\frac{\rho \propto s}{t}\right)^{1/4} = \left(\frac{1}{K_t}\right)^{1/4} D$$

In this form D is the x variable, $(\rho \propto s/t)^{1/4}$ is the y variable, and $(1/K_t)^{1/4}$ is the regression coefficient. The results are plotted in Figure 4. Using a value of s equal to $[(0.02 \times \%\ \text{stenosis}) - (0.0001 \times \%\ \text{stenosis}^2)]^2$ results in a nonlinear relation, which

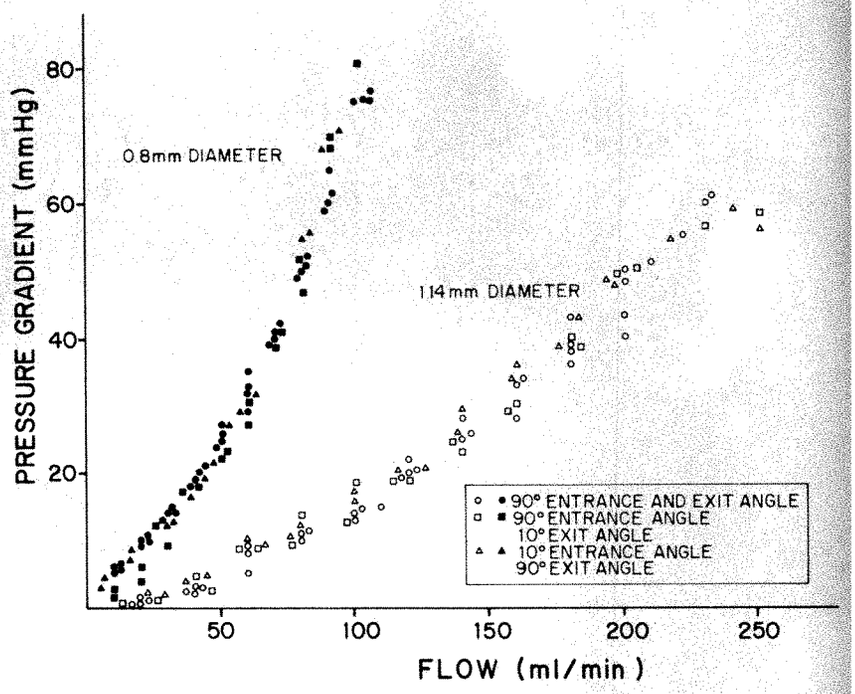


FIGURE 7. Effect of changing the exit angle of the stenosis on the relation between pressure gradient and flow. All stenoses were 5 mm long. For each diameter, values were determined for a stenosis with entrance and exit angles of 90°, and a stenosis with one angle of 10° and one angle of 90°. By reversing flow this same stenosis then had either a 90° or 10° exit angle. All stenoses were molded and studied in duplicate.

indicates that this is not the proper value for s. However, when a value of 1.0 is used for s, the relation is linear, indicating that 1.0 is the proper value for s. The regression coefficient for this linear relation is 4.91, from which K_t is calculated to be 0.0017 (95 percent confidence limits of 0.0016 to 0.0018), the same as the theoretically derived K_t of equations 4 and 5. Thus, under the conditions and dimensions of stenosis used in this study, with percent stenoses as low as 26 percent, the turbulent component of the pressure gradient is calculated by assuming that all of the kinetic energy within the stenosis is dissipated in turbulence at the stenosis exit. Percent stenosis has no direct influence on the pressure gradient.

The foregoing relations were all determined in stenoses with exit angles of 90°. It is conceivable that less acute angles could decrease the exit turbulence and in turn the pressure gradient. To test this possibility, the pressure gradient-flow values of stenoses identical except for exit angles of either 90° or 10° were compared (Fig. 7). As is apparent, there was no significant difference in values, indicating that, at least between 90° and 10°, variations in angle have no influence on the pressure gradient.

Pressure gradient due to nonturbulent intrastenotic flow: The component of pressure gradient due to nonturbulent intrastenotic flow is represented by nF in equation 1. According to equation 7, n should be equal to $K_n \mu L D^{-4}$. Each component of this term was tested separately to determine its actual influence on n.

Because n *should be dependent on the viscosity* (μ) *of blood,* this dependence was tested by comparing the n coefficient of blood to the n coefficient of water determined in the same stenoses. The water was studied at 20° C at which temperature the viscosity of water is 0.010 poise.[5] Because K_n, L and D were identical for blood and water in each stenosis, the ratio of the n coefficient of blood to that of water multiplied by 0.01 should equal the absolute viscosity of blood. The mean ratio of the n coefficient of blood to the n coefficient of water is 2.50 ± 0.30 (standard error). Thus the absolute viscosity of blood under these conditions is 0.025 poise. This value compares favorably with the absolute viscosity of blood reported by others[7,11,12] to be about 0.023 to 0.035.

The second factor that should affect n *is stenosis length.* To test this dependence the n coefficient of each stenosis was divided by the average n value of the 20 mm long stenoses of the same diameter. This normalized n value was then plotted against stenosis length in Figure 5. As expected, the relation was linear; however, the intercept on the length axis is at −2.3 mm. This is consistent with the empiric concept of "inlet length" in which the additional pressure loss caused by the flattened velocity profile at the inlet is incorporated into the Poiseuille equation. This is done by assuming an increase in the actual length by an "inlet length."[3,7] Hence the length in equations 6 and 7 is now represented by L + 2.3.

The last variable on which n *should be dependent is diameter of the stenosis.* To test this dependence, in each stenosis the diameter was compared with the value of n modified by the previously delineated variables of length and viscosity. If this relation is quantitated by the theoretically derived K_n, then the hypothesis is validated. To show this relation most clearly, equation 7 is rearranged to the regression equation:

$$\left(\frac{\mu\,(L + 2.3)}{n}\right)^{1/4} = \left(\frac{1}{K_n}\right)^{1/4} D$$

In this form D is the x variable, $(\mu\,(L + 2.3)/n)^{1/4}$ is the y variable, and $(1/K_n)^{1/4}$ is the regression coefficient. The results are plotted in Figure 6. The linear relation substantiates the dependence of n on D^{-4}. The regression coefficient is 1.18 from which K_n is calculated to be 0.52 (95 percent confidence limits of 0.50 to 0.53), essentially the same as 0.51, the theoretically derived value. Thus the use of the Poiseuille equation under these circumstances is validated.

The formula for total pressure gradient (of 37° C blood at a hematocrit of 40 percent for stenoses greater than or equal to 26 percent) is:

$$PG = [K_t \rho \alpha s D^{-4} F^2] + [K_n \mu (L + 2.3) D^{-4} F]$$

or

$$PG = [(0.0017)(1.06)(0.034L + 1.33)(1.0) D^{-4} F^2] + [(0.52)(0.025)(L + 2.3) D^{-4} F] \quad (9)$$

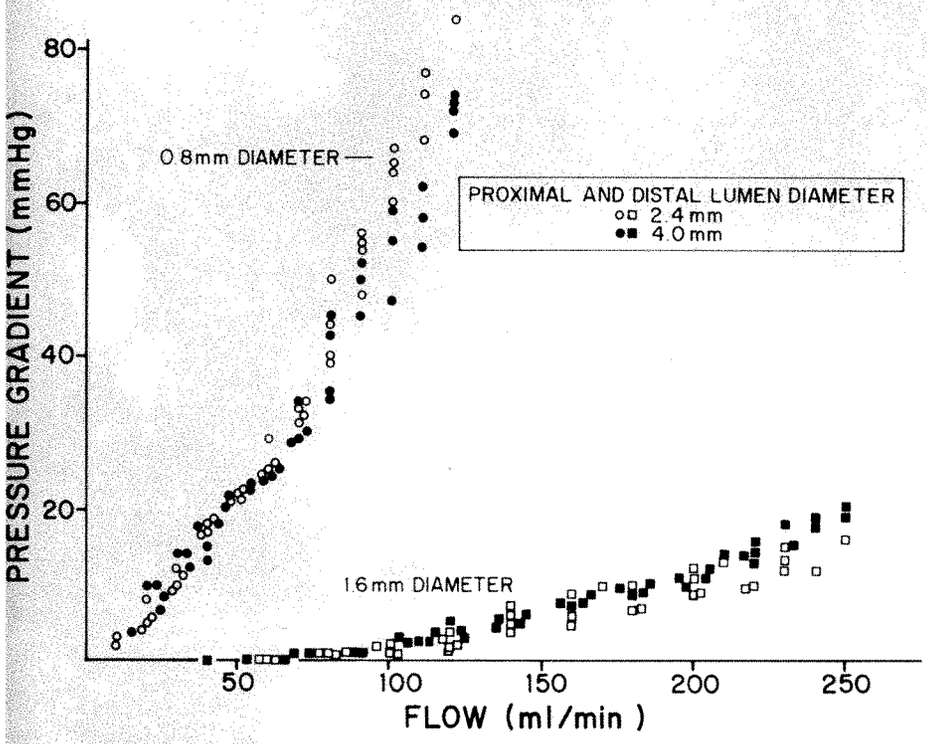


FIGURE 8. Effect of changing the pre- and poststenotic lumen diameter on the relation between pressure gradient and flow. Because absolute dimensions of the stenoses were not changed, this graph shows the effect of changing "percent stenosis" while keeping absolute dimension of each stenosis constant.

Percent stenosis: The relative decrease in the diameter of a stenosis compared with the unstenosed portion of the vessel, commonly expressed as "percent stenosis," is frequently used to estimate the hemodynamic severity of a stenosis. The results presented so far in this study indicate that absolute dimensions of a stenosis are the determinants of pressure gradient. To determine whether the relative reduction in diameter has any effect on pressure gradient independent of absolute dimensions, the pressure gradient-flow values of stenoses were compared when only the diameter of the pre- and poststenotic lumens was changed. Thus percent stenosis was changed while absolute dimensions of the stenosis were held constant (Fig. 8). It is apparent that absolute dimensions and not percent stenosis determine hemodynamic severity.

Discussion

Previous studies on stenoses-flow relations: Most studies on the hemodynamic effect of arterial stenosis are observations on the relation between a graded stenosis of the in vivo artery and the diminution of flow through the artery.[4,13–18] In general these studies have shown that in the resting state a decrease in vessel diameter of about 80 percent is necessary to cause a reduction in flow, but if the distal bed is vasodilated, a decrease in vessel diameter as small as 50 percent can cause a reduction in the hyperemic flow.[4,13,17,18] Other studies have shown that flow through the distal bed is determined by its perfusion pressure,[19,20] and that a stenosis decreases flow by decreasing this perfusion pressure.[20] For a fixed resistance of a distal bed, flow is directly dependent on perfusion pressure in the distal bed. However, if the distal bed is not maximally vasodilated, the bed regulates itself in response to changes in perfusion pressure in an attempt to maintain coronary flow constant.[19,20] The relation between the stenosis and flow is therefore dependent on both the loss of perfusion pressure caused by the stenosis, that is, the pressure gradient, and the distal bed resistance.[20] Because the hemodynamic effect of the stenosis itself is mediated entirely by the pressure gradient it causes, the most specific way to study the effect of variables on a stenosis is to study the effect these variables have on the gradient across the stenosis.

May et al.[3,4] suggested that the pressure gradient across a stenosis is equal to the sum of the gradient due to nonturbulent flow through the body of the stenosis and the gradient due to turbulence at the exit from the stenosis. Using a formula similar to the one used in our study, they approximated the pressure gradients actually found across stenoses of the femoral arteries of dogs. However, in trying to extend the applicability of their formula, they estimated that an 11 percent reduction in the diameter of a coronary artery would constitute a critical lesion. This value is inconsistent with clinical and other experimental results.[18,21] This discrepancy is apparently a result of their assumption that the viscosity of blood was 4 poise instead of the more appropriate value of 0.04 poise. Seeley and Young[1] studied the effect of dimensions of a stenosis on the pressure gradient in a model system using a glycerol and water solution. The dimensions of their system were larger than those of our system, with the unobstructed lumen measuring 12.7 mm in diameter and the most severe stenosis 3.2 mm in diameter. Nevertheless their results were similar to ours in that they found that the pressure gradient could be estimated by assuming nonturbulent flow through the body of the stenosis and turbulent flow at the exit. Young et al.[22,23] then found that by using the nonturbulent-turbulent model and

determining the equation coefficients by in vitro testing, they could accurately predict the actual pressure gradients found across stenoses in the femoral and carotid arteries of dogs. Logan[24] studied the pressure gradient-flow relation of excised human coronary arteries and attempted to define the relation in a linear equation. He found that the equation coefficients increased with increasing flow, a finding consistent with the effect of the unaccounted factor of turbulence. Berguer and Hwang[6] studied the pressure gradient-flow relation of stenoses in the aortas of dogs and defined the relation by assuming that all of the pressure gradient was due to turbulence. They neglected the component of the gradient due to nonturbulent flow, a procedure that, for practical purposes, is valid at the flow rates studied.

Flow pattern through a stenosis: This is critical to our hypothesis. Several lines of evidence indicate that flow is nonturbulent through the body of the stenosis and becomes turbulent at the exit from the stenosis. The Reynolds number is frequently used to estimate when turbulence is likely to occur. The Reynolds number is the product of velocity, diameter, density and 1/viscosity. In tubes leading from a reservoir, a situation similar to a stenosis, turbulence usually does not occur with a Reynolds number of less than 2,000.[5,7] At the maximal flow rate of each stenotic diameter in this study the Reynolds numbers ranged from approximately 500 to 1500; thus, nonturbulent flow in the body of the stenosis is to be expected. However, at the exit from a stenosis turbulence can occur at a much lower Reynolds number, with a value as low as 140 having been reported.[25] In this study, we have assumed that exit turbulence occurs at all rates of flow. This is probably not true at very low flow rates. Nevertheless, by visual inspection the pressure gradient-flow values do not significantly deviate from the fitted curves at these low flow rates. This may be because at low flow rates the assumed turbulence contributes relatively little to the total pressure gradient by comparison with its contribution at high flow rates. Other evidence for our assumed flow pattern is the work of Robbins and Bentov,[2] who visually studied the flow pattern through stenoses approximately the size of those found in the coronary artery. Their pictures show nonturbulent flow through the body of the stenosis with turbulence at the exit. Finally, our hemodynamic data, in which the total pressure gradient is the sum of the gradients expected from the nonturbulent and turbulent flow, support the hypothesized flow pattern.

The flow profile at the inlet of a stenosis is flat; that is, the velocity is the same across the diameter of the stenosis. As flow progresses down the stenosis, laminar flow begins to develop. When laminar flow is fully developed, the velocity is 0 at the periphery and highest in the center. The length of the tube from the reservoir to full development of the flow profile is usually calculated as the product of the diameter, Reynolds number and a variously reported constant of 0.03 to 0.065.[5,7,24] At maximal flow rates this length would be longer than that in any of the stenoses studied. From a practical standpoint, the important aspect is how this developing flow profile differs from a fully developed profile in its pressure-flow relations. The poorly developed flow profile near the inlet causes an increase in the pressure gradient over that predicted by the formula for nonturbulent flow. An empiric way to incorporate this additional gradient is to assume mathematically an increase in the actual length by an "inlet length." Two suggested "inlet lengths" are approximately 0.8 and 0.3 times the diameter.[3,7] In this study, for simplicity, we studied stenoses of all diameters together and derived a composite "inlet length" of 2.3 mm. The extent of development of the flow profile also affects the pressure gradient due to turbulent flow because the kinetic energy in a fully developed flow profile is twice that in a flat profile. Empirically we assumed that the flow profile was fully developed in all stenoses with a length of 20 mm. Using this assumption we found that the pressure gradient did increase as expected with increasing stenosis length. The data are only approximate, however, because the diameter of the stenoses was not incorporated into the calculation.

Principal determinants of the pressure gradient across a stenosis: These are the blood flow through the stenosis and the length and diameter of the stenosis. To understand the relevance of flow and length of stenosis to the pressure gradient, it is useful to consider separately the relation of these two variables to the turbulent and nonturbulent components of the pressure gradient. In Figure 9, the turbulent and nonturbulent components of the pressure gradient across a stenosis with a diameter of 1.3 mm are plotted separately. The solid line represents a 2 mm long stenosis and the dotted line a 20 mm long stenosis. For a given length of stenosis, the nonturbulent component of the pressure gradient is related to flow linearly whereas the turbulent component is related to flow squared. Consequently at low rates of flow the contribution of the nonturbulent component of the pressure gradient is large relative to the turbulent component. However, at high rates of flow the relative contribution of the nonturbulent component becomes progressively less. From this graph, it is apparent that the rates of flow through the coronary arteries are in the flow range where both the nonturbulent and turbulent components of the pressure gradient are significant. At lower rates of flow, such as those occurring in vessels smaller than the major coronary arteries, the turbulent component is negligible. At higher rates of flow, such as those occurring across a stenotic heart valve, the nonturbulent component is negligible. Thus the formula for determining the size of the orifice of stenotic heart valves assumes that all of the pressure gradient is due to turbulence.[26]

Because length of stenosis has a greater effect on the nonturbulent than on the turbulent component of the pressure gradient, and because the nonturbulent component is relatively more significant at low rates of flow, a change in length of stenosis will have a greater effect at low than at high rates of flow. Although the absolute values for pressure gradient in Figure 9 are calculated for a stenosis 1.3 mm in diameter, the relative contribution of the pressure gradient due to turbulent and

nonturbulent flow is applicable to stenoses of all diameters, because diameter contributes equally to the turbulent and nonturbulent components.

The most important determinant of pressure gradient across a stenosis is the diameter of the stenosis. Figure 10 shows the relation between diameter of the stenosis and the pressure gradient at different flow rates and lengths of stenosis. It is apparent that a relative change in diameter has a far greater influence than a change in length.

Percent stenosis and hemodynamic significance of the stenosis: The relative reduction in luminal diameter caused by a stenosis, usually expressed as percent stenosis, is commonly used clinically to judge the

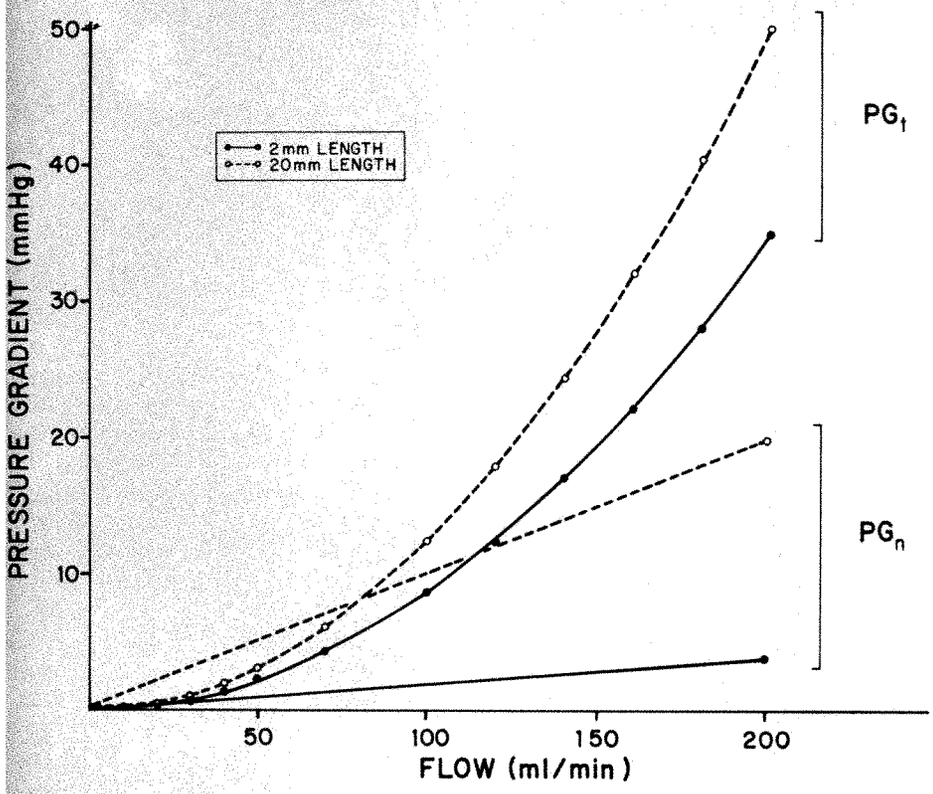


FIGURE 9. Relation of pressure gradient to flow plotted separately for the turbulent (PG_t) and nonturbulent (PG_n) components of the pressure gradient in stenoses 2 and 20 mm long. The diameter of the stenoses is 1.3 mm. Because the diameter affects PG_t and PG_n equally, the relation of PG_t to PG_n at each rate of flow is the same for stenoses of all diameters.

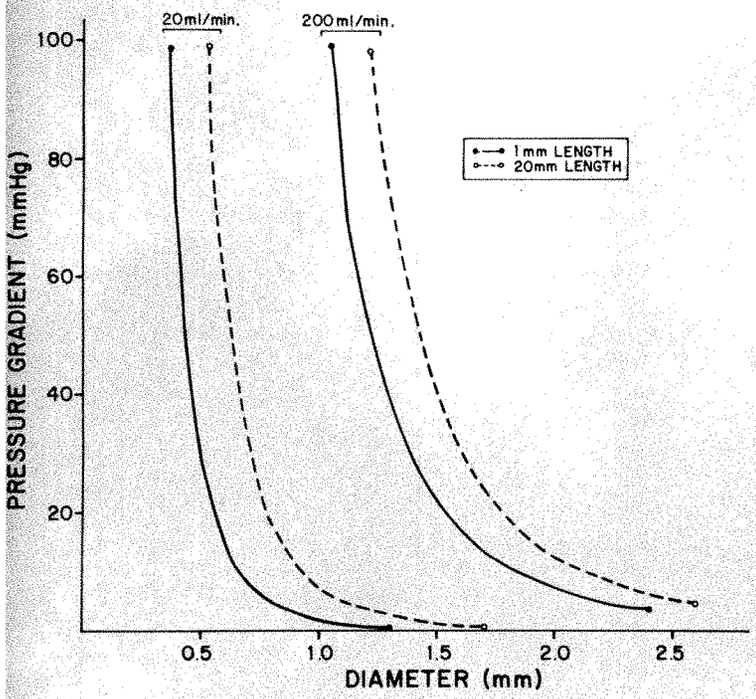


FIGURE 10. Relation of pressure gradient to diameter of stenosis at extremes of flow rates and lengths of stenosis likely to be found in the coronary circulation.

hemodynamic significance of the stenosis. The rationale for this approach is partially based on a well known, theoretically derived formula used in hydraulic engineering that states that the energy loss due to a sudden expansion in a pipeline is proportional to the square of the difference in velocities between the intrastenotic and downstream nonstenotic flow.[5] This formula is equivalent to using an s value in our equations 4, 5 and 9 equal to $[(0.02 \times \% \text{ stenosis}) - (0.0001 \times \% \text{ stenosis}^2)]^2$. Therefore if this relation were appropriate, a measurement of the percent stenosis would be necessary to determine the pressure gradient. However, the conditions assumed in the development of the formula are not necessarily applicable to the flow of blood. Berguer and Hwang[6] concluded that the energy loss of blood flow through a stenosis due to turbulence is proportional only to the square of the intrastenotic velocity, which is equivalent to using an s value in our equations equal to 1.0. Our results (Fig. 4) support this conclusion and hence the propriety of disregarding the percent stenosis as a direct determinant of the pressure gradient. Our results show that an s value of 1.0 is appropriate with a percent stenosis value as low as 26 percent (stenotic lumen 2.36 mm, nonstenotic lumen 3.2 mm); however, obviously at some value for percent stenosis between 0 and 26 percent, turbulence will not develop and our formulas will be invalid. The increased energy loss with blood compared with that predicted from the hydraulic engineering formula may possibly be explained by the observation that the addition of erythrocytes to plasma increases the intensity of turbulence at an exit from a stenosis.[27]

Use of percent stenosis to estimate pressure gradient: Although percent stenosis has no direct effect on the pressure gradient, the use of percent stenosis to estimate the pressure gradient may be appropriate under two conditions. One condition is that the component of the pressure gradient due to nonturbulent flow be negligible. The second is that the different arteries have a constant relation between their volume of flow and nonstenotic luminal diameter so that the velocities of flow in the nonstenotic portion of different arteries are equal. If the latter velocities are equal, then for a given percent stenosis the flow velocities within the stenosis will be equal, regardless of the absolute size of the artery or the volume of flow. If the intrastenotic velocities are equal, then the kinetic energy, and hence the pressure gradients due to turbulence, will be equal. For perspective, an intrastenotic velocity of 160 cm/sec will result in a gradient due to turbulence of 10 mm Hg (assumed $\propto$ of 1.0). Approximately equal velocities have been reported from different major arteries in man. At rest, peak flow velocity values (in cm/sec) during the cardiac cycle have been reported to be 66 and 45 in the aorta,[28,29] 57 in the pulmonary artery,[28] 30 in the carotid artery[30] and 35 in the coronary artery.[31] Whether the arterial flow velocity is constant enough between the different coronary arteries in different patients to provide a valid basis for using the percent stenosis to estimate pressure gradient is uncertain. Another potential problem with using the percent stenosis approach is deciding which segment of an apparently normal vessel should be used for reference. If the reference vessel itself should have unrecognized disease, then estimations of stenosis based on this segment would be in error. To our knowledge the magnitude of this error has never been systematically evaluated; however we, as well as others,[32] consider it a potentially significant problem. Because of these uncertainties and the fact that the percent stenosis approach does not account for the component of the pressure gradient due to nonturbulent flow, clinical estimates of significance of stenosis based on absolute dimensions are theoretically more accurate than those based on percent stenosis.

Pressure gradient-flow relation: We studied the relation of the pressure gradient to flow under steady state conditions rather than under pulsatile conditions characteristic of the intact circulation. When the column of blood in the nonstenotic vessel is positively or negatively accelerating there is a component of pressure gradient proportional to the rate of acceleration and the distance between the measuring points.[33] Young and co-workers[22,34] have shown that interposing a stenosis between the measuring points has little influence on the component of pressure gradient due to acceleration. Because interposing a stenosis adds only those pressure gradient factors present during steady flow, increasing stenosis has the effect of decreasing the sensitivity of the total pressure gradient to acceleration. The pressure gradient due to acceleration is small. In the aorta, where the rate of acceleration should approximate that in the coronary artery, the pressure gradient at peak acceleration is about 3 mm Hg/cm.[28] Furthermore, in the presence of significant stenosis the in vivo coronary flow becomes less pulsatile.[35] Consequently the effect of acceleration in the coronary circulation is usually neglected.

However, even if the instantaneous relation between pressure gradient and flow is considered to be identical during steady state and pulsatile flow conditions, this does not mean that during pulsatile flow the mean pressure gradient-flow relation is the same as the instantaneous pressure gradient-flow relation. This is because the relation of pressure gradient to flow is nonlinear. For example, consider a stenosis where the nonturbulent component is negligible and the t coefficient is 1, giving the equation $PG = F^2$. If a flow of 1 ml/min is steady, then the pressure gradient is 1. If the flow is then made pulsatile such that flow occurs during one third of the cycle, the intermittent flow rate must be 3 to maintain a mean flow of 1. The pressure gradient during flow would be 9, giving a mean pressure gradient of 3. Thus the transition from steady to pulsatile flow caused the mean pressure gradient to increase threefold without a change in the mean flow. Hence in any study of the stenosis pressure gradient-flow relation, the instantaneous relation and the pulse wave form must be considered.

Clinical implications: Results obtained from models should be extrapolated to the clinical setting with caution; however, a potential approach for clinical use can be suggested. Equation 9 and Figure 10 show that the three determinants of the pressure gradient, in de-

scending order of importance, are diameter of the stenosis, flow through it and length of the stenosis. Diameter and length of the stenosis can be measured angiographically by comparison with a standard such as the diameter of the catheter. Flow through the stenosis can be estimated by multiplying the coronary flow per gram of myocardium times the mass of myocardium supplied by the stenotic vessel. The flow/g ratio can be estimated from the fact that the normal mean coronary flow in the resting state is about 0.75 ml/min per g.[36,37] The mass supplied by the vessel can be estimated by first measuring or estimating the total left ventricular mass of the patient, based on the normal value of 100 g/m^2 of body surface area,[38] and then estimating the fraction of the total mass supplied by the stenotic vessel.

In Figure 10, the relation of pressure gradient to diameter of the stenosis is plotted for extremes of stenosis length and flow likely to be found clinically. The "critical" diameter of a stenosis ranges between approximately 0.6 and 2.0 mm and chiefly depends on flow. Obviously this approach to assessment of significance of a stenosis needs further validation, and many problems, such as the influence of irregular geometric features of a stenosis on the pressure gradient, need to be solved. In addition, greater accuracy in the measurement of dimensions and flow would improve the precision of the approach. Brown et al.[32] recently reported a computerized technique to improve the accuracy of angiographic measurement of dimensions of a coronary stenosis.

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Idiopathic Hypertrophic Subaortic Stenosis in the Young

GARRICK I. FIDDLER, MB, MRCP
ABDUL J. TAJIK, MD, FACC
WILLIAM H. WEIDMAN, MD
DWIGHT C. McGOON, MD, FACC
DONALD G. RITTER, MD, FACC
EMILIO R. GIULIANI, MD, FACC

Rochester, Minnesota

Thirty-six young patients with idiopathic hypertrophic subaortic stenosis were studied. Twenty-seven patients were male and 9 female, and their mean age was 11.3 years (range 5 months to 20 years). Twenty-three patients (64 percent) had symptoms, the most common being dyspnea, angina and syncope. Diagnostic difficulties were encountered frequently in younger patients, especially those with right heart involvement, and in asymptomatic patients with murmurs suggestive of other cardiac defects. Patients were classified retrospectively into three groups on the basis of management. The first group consisted of 16 patients who were operated on; 4 of these patients died, 1 operatively and 3 suddenly late postoperatively (at 1.6, 2 and 10 years). The 12 long-term survivors (average follow-up period 6.2 years) have had good relief of symptoms. The second group comprised seven patients treated with propranolol; none of these died. The 13 patients in the third group received no therapy; 7 of these patients died, 6 suddenly and 1 from congestive cardiac failure. Idiopathic hypertrophic subaortic stenosis is a serious disorder that may present at any age and that may be difficult to diagnose. All patients with this disorder should be treated with propranolol; surgical intervention, although it does not totally abolish the risk of sudden death, appears to offer symptomatic improvement in most cases over a long-term follow-up period.

Idiopathic hypertrophic subaortic stenosis is a primary myocardial disease of unknown cause characterized by asymmetric hypertrophy of the left ventricle, affecting mainly the ventricular septum.[1] Left ventricular outflow tract obstruction is usually present,[2,3] and occasionally the right ventricular outflow tract may be obstructed, either as an isolated phenomenon or in association with left-sided involvement.

The pathologic features of idiopathic hypertrophic subaortic stenosis were first recognized by Schmincke[4] in 1907. Fifty years later, the clinical and pathologic findings of an unusual form of left ventricular outflow tract obstruction were described by several investigators.[5–7] The disease has since received considerable attention, and its clinical, electrocardiographic, roentgenographic and echocardiographic features have been well defined.[8–12] However, little is known about the presentation, course and management of this disease in the young patient. Since our initial report,[13] we have added adolescents to our study group, and this report presents a detailed account of the disease in 36 children and adolescents.

Material and Methods

From 1959 through 1975 idiopathic hypertrophic subaortic stenosis was diagnosed at the Mayo Clinic in 36 patients aged 20 years or younger; 27 were male and 9 female. The mean age at the time of diagnosis was 11.3 years (range 5 months to 20 years). The diagnosis was confirmed at cardiac catheterization and angiography in 32 patients using the criteria described by Braunwald et al.[8] Clinical findings and typical echocardiographic features[11] confirmed the

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Manuscript received March 28, 1978; revised manuscript received May 23, 1978, accepted May 24, 1978.

Address for reprints: Abdul J. Tajik, MD, Mayo Clinic, Rochester, Minnesota 55901.

TABLE I

Symptoms in 23 of 36 Young Patients With Idiopathic Hypertrophic Subaortic Stenosis

	Patients no.	Patients %
Dyspnea on exertion	14	39
Angina	10	28
Syncope	3	8
Fatigue	2	6
Paroxysmal arrhythmia	2	6
Congestive heart failure	1	3

diagnosis in two patients, and the two remaining patients were found to have the disease at autopsy. Three patients (two male and one female) had a family history of confirmed idiopathic hypertrophic subaortic stenosis in first-degree relatives.

Clinical Features

Symptoms: Thirteen (36 percent) of the 36 patients were asymptomatic, and 23 (64 percent) had symptoms that ranged from mild exertional dyspnea to angina and syncope (Table I). Fourteen patients had mild symptoms (New York Heart Association functional class II)[14]; their mean age was 12 years. The other nine symptomatic patients had moderate to severe symptoms (functional classes III and IV); their mean age was 11.4 years.

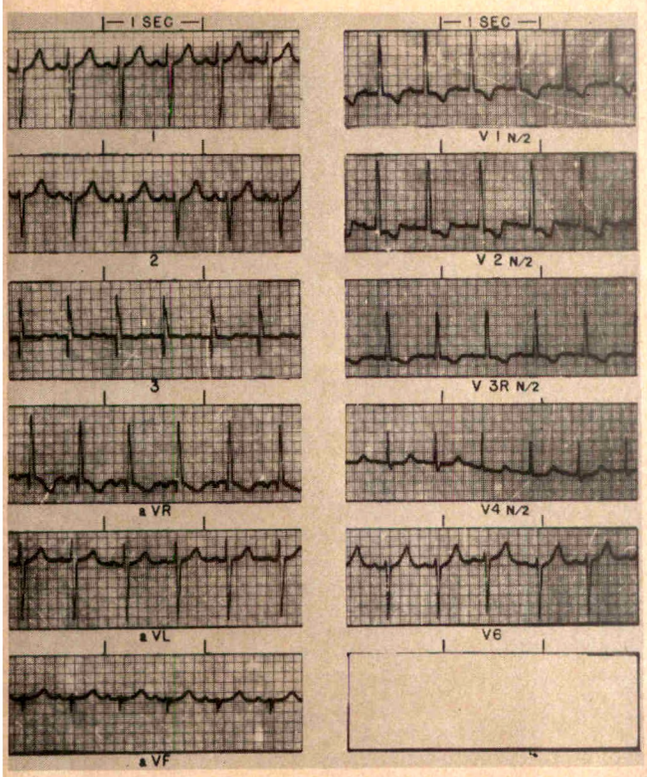


FIGURE 1. Electrocardiogram from a 16 month old boy with pressure gradients exceeding 100 mm Hg across both ventricular outflow tracts. The frontal plane QRS axis is +190° with a clockwise loop. Ventricular depolarization forces in the horizontal plane are directed anteriorly and to the right. There are 52 mm R waves and inverted T waves in leads V_3R to V_2, indicating severe right ventricular hypertrophy. Left ventricular forces are masked. N/2 = half standardization.

TABLE II

Age at Discovery of a Systolic Murmur in 36 Young Patients With Idiopathic Hypertrophic Subaortic Stenosis

Age	Patients (no.)
Birth to 1 week	5
1 week to 5 years	18
5 to 10 years	3
11 to 15 years	6
16 to 20 years	4

TABLE III

Electrocardiographic Findings in 36 Young Patients With Idiopathic Hypertrophic Subaortic Stenosis

	Patients (no.)
Left ventricular hypertrophy	30
Abnormal ST-T waves	13
Right ventricular hypertrophy	3
Biventricular hypertrophy	2
Abnormal Q waves	7
Right axis deviation	4
Left axis deviation	2
Preexcitation pattern	2
Right bundle branch block	1
Normal	1

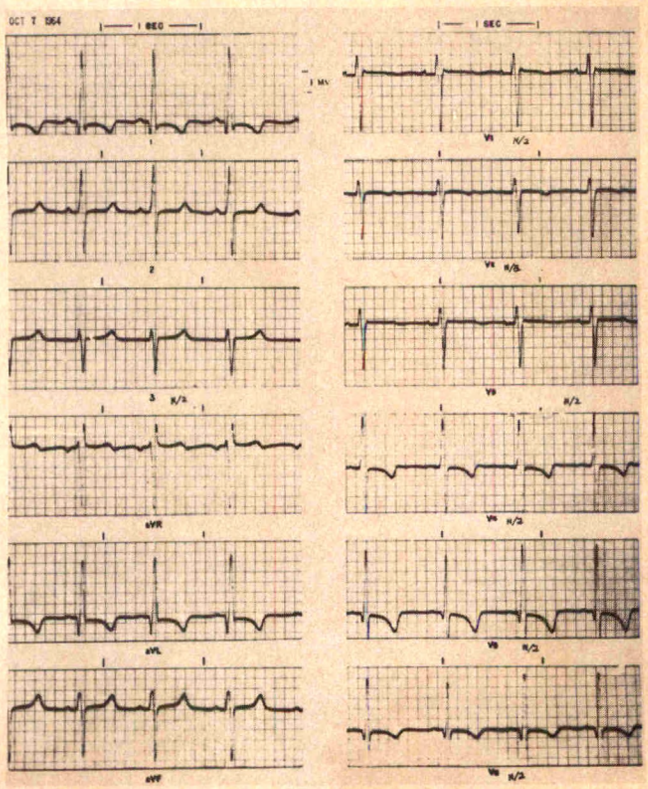


FIGURE 2. Electrocardiogram from an 11 year old boy with a pressure gradient of 160 mm Hg across the left ventricular outflow tract. The QRS axis in the frontal plane is −20° with a counterclockwise loop. The T axis is +125°. Ventricular depolarization forces in horizontal plane are directed to the left and posteriorly with a 44 mm R wave and an 8 mm Q wave in lead V_6. The T waves are inverted in leads V_4 through V_6. These findings indicate severe left ventricular hypertrophy. N/2 = half standardization.

Physical findings: All patients had a systolic cardiac murmur of the basal "ejection" or apical pansystolic type, or both. In 15 patients (42 percent) a precordial systolic thrill was present. In more than half of the patients the systolic murmur was discovered between birth and age 5 years (Table II). The Valsalva maneuver was performed in 10 patients; the intensity of the murmur increased in 8 of these patients but decreased in 2. Ten patients (28 percent) had a diastolic murmur, including six patients with an apical mid diastolic and three with an early diastolic murmur heard at the left sternal border. One patient with an associated secundum atrial septal defect had a tricuspid diastolic flow murmur at the lower right sternal border. An early systolic ejection click was heard in one patient later found to have associated mild aortic valve stenosis.

Idiopathic hypertrophic subaortic stenosis was suspected clinically in 11 patients (31 percent), all of whom were older than the average age of the group. Diagnostic difficulties were encountered often in younger patients, especially in the five patients found to have right heart involvement on later investigation. Two of these five patients were less than 1 year old; one of these was thought to have tetralogy of Fallot and another, severe pulmonary valve stenosis. Other frequent initial diagnoses were congenital mitral regurgitation and ventricular septal defect.

Electrocardiographic findings: All patients had sinus rhythm. The electrocardiogram was abnormal in all but one patient. Left ventricular hypertrophy with or without "strain" (ventricular repolarization abnormalities), the most common abnormality, was present in 30 patients (83 percent). Seven patients (19 percent) had Q waves with an abnormal mean axis and amplitude. Table III summarizes the abnormalities and Figures 1 and 2 show representative tracings.

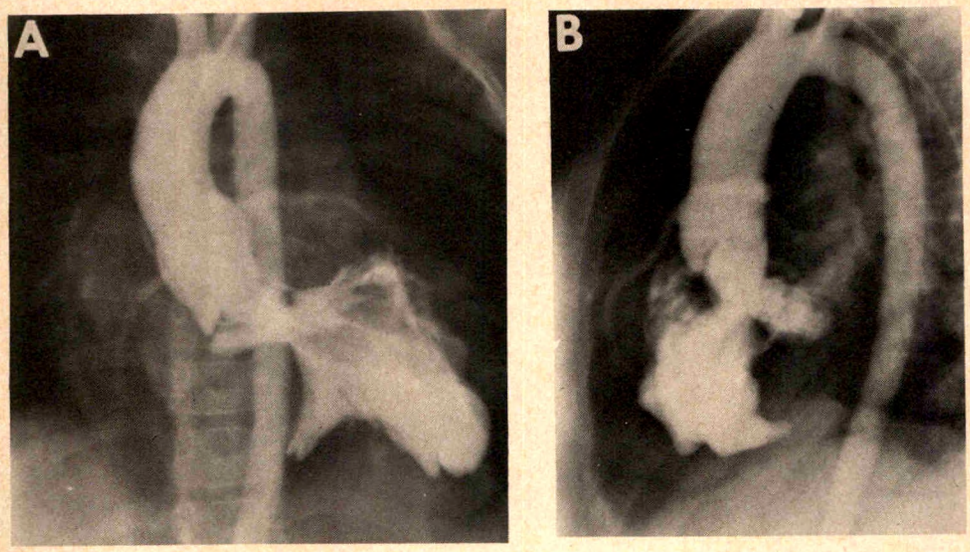


FIGURE 3. Left ventricular angiograms in a 4 year old boy. Anterior (**A**) and lateral (**B**) projections show gross irregular hypertrophy of the left ventricle with deformed cavity. Note the pronounced hypertrophy of muscle in the region of the ventricular septum and the posterior wall of the left ventricle.

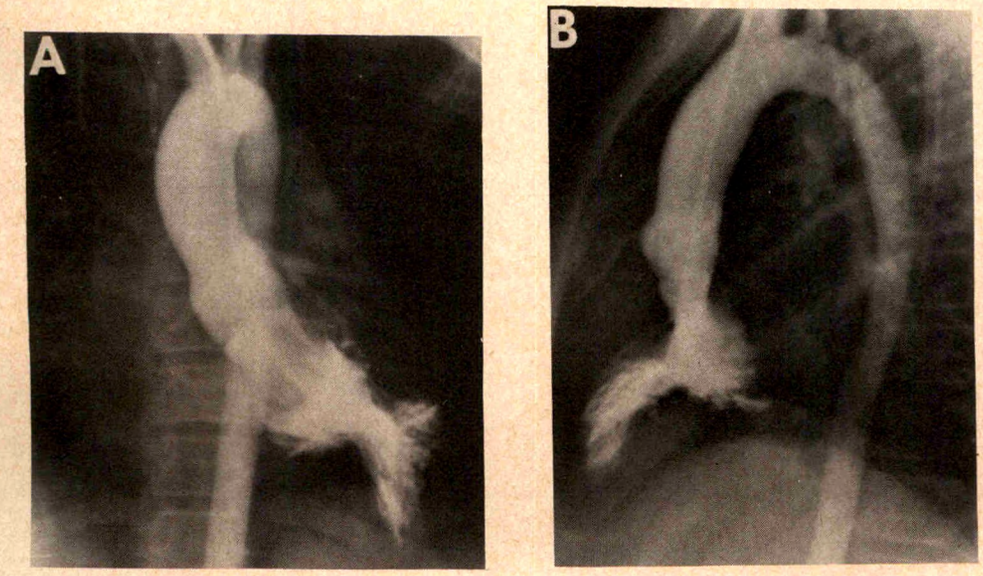


FIGURE 4. Left ventricular angiograms in an 11 year old girl. Anterior (**A**) and lateral (**B**) projections show the hypertrophied left ventricle with an angulated cavity. The hypertrophy involves mainly the mid and basal parts of the left ventricle and spares the left ventricular apex.

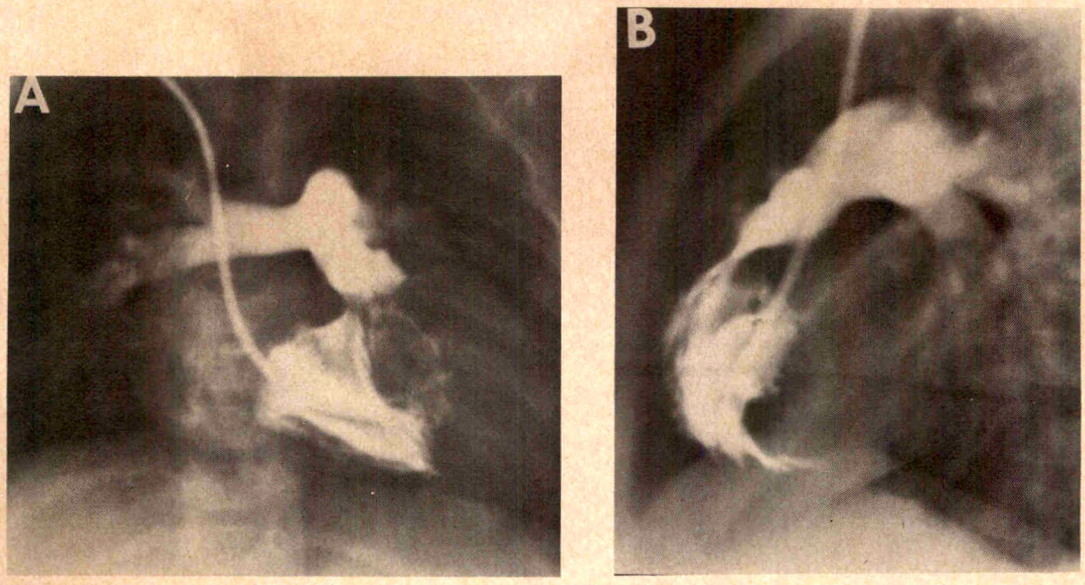


FIGURE 5. Right ventricular angiograms in a 17 month old boy. Anterior (**A**) and lateral (**B**) projections show the narrowing of the outflow tract that results from bulging of the hypertrophied septum into the right ventricle.

Roentgenographic findings: The cardiac silhouette in the chest roentgenogram was normal in 9 patients (25 percent); in the other 27 patients (75 percent) it was abnormal and showed various degrees of cardiomegaly, mainly involving the left ventricle and left atrium.

Hemodynamic and angiographic findings: Hemodynamic data were available in 31 of the 32 patients who underwent cardiac catheterization. In 29 patients the basal peak systolic gradient between the left ventricle and the systemic artery averaged 71 mm Hg (range 15 to 160). The two patients who had no measurable gradient in the basal state had a gradient of 50 and 80 mm Hg with provocation (isoproterenol infusion). The average left ventricular end-diastolic pressure was 16 mm Hg (range 3 to 31), and the average cardiac index was 4.3 liters/min per m^2 (range 2.5 to 9.0). Five patients had a peak systolic gradient across the right ventricular outflow tract averaging 69 mm Hg (range 28 to 106). In 32 patients biplane roll film or single plane left ventricular cineangiography was performed, disclosing various degrees of deformity of the cavity (Fig. 3 and 4). Right ventricular angiography was performed in four patients, revealing septal hypertrophy encroaching on the right ventricular outflow tract in all four (Fig. 5).

Echocardiographic findings: Echocardiography, performed in six patients, revealed features typical of idiopathic hypertrophic subaortic stenosis—in all six asymmetric septal hypertrophy and systolic anterior motion of the anterior leaflet of the mitral valve. The two patients in this subgroup seen most recently were asymptomatic, and the diagnosis was based on clinical and echocardiographic findings alone.

Complications and associated findings: Two patients, one with an electrocardiographic pattern of preexcitation, experienced symptomatic arrhythmias that required therapy. Infective endocarditis due to Listeria monocytogenes was documented in one patient. Serum levels of the enzyme creatine kinase, determined in nine patients, were elevated in five. Six types of associated conditions were seen in 10 patients (Table IV).

TABLE IV

Associated Conditions in 10 of 36 Young Patients With Idiopathic Hypertrophic Subaortic Stenosis*

	no. of Patients
Multiple lentigines	4
Secundum atrial septal defect	2
Coarctation of aorta	2
Aortic valve stenosis (mild)	2
Pierre Robin syndrome	1
Tuberous sclerosis	1

* Two patients had more than one associated condition.

TABLE V

Hemodynamics and Functional Class of 36 Young Patients With Idiopathic Hypertrophic Subaortic Stenosis

Management	Mean Gradient (mm Hg)	Mean LVEDP (mm Hg)	NYHA Functional Class (no. of Patients)* I	II	III, IV
Surgical (16 patients)	91	16	4	5	6 (1)
Propranolol (7 patients)	42	14	1 (2)	4	. . .
Observation (13 patients)	41	17	6	4 (1)	1 (1)

* Figures in parentheses indicate patients without hemodynamic data.

LVEDP = left ventricular end-diastolic pressure; NYHA = New York Heart Association.

TABLE VI

Results in Three Management Groups of Young Patients With Idiopathic Hypertrophic Subaortic Stenosis

	Surgical Group (16 patients)	Propranolol Group (7 patients)	Observation Group (13 patients)
Follow-up interval			
Mean	5.3 yr	3.8 yr	5.2 yr
Range	1 to 15 yr	8 mo to 8 yr	5 mo to 11 yr
Functional class before/after intervention (no. of patients)			
I	4/7	3/4	6/4
II	5/5	4/3	5/2
III, IV	7/0	0/0	2/0
Deaths (no.)			
Total	4	0	7
Operative	1	0	0
Late sudden	3*	0	6
Congestive heart failure	0	0	1

*These deaths occurred 1.6, 2 and 10 years, respectively, after operation.

TABLE VII

Sudden Deaths (6 Cases) Among 13 Young Untreated Patients With Idiopathic Hypertrophic Subaortic Stenosis

Age at Death (yr)	Follow-Up (yr)	NYHA Functional Class	Basal LV Pressure Gradient (mm Hg)	LVEDP (mm Hg)
5/12	4/12	III	46	15
9	8.3	II	20*	6
10	3.4	II	19	31
13	2.6	II	9	18
15	7.8	I	85	24
16	5/12	II	90	18

* Also a right ventricular pressure gradient of 64 mm Hg.
LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; NYHA = New York Heart Association.

The two patients with aortic coarctation underwent successful repair and, because of a persisting murmur, idiopathic hypertrophic subaortic stenosis was diagnosed, respectively, 2 and 7 years later in these two patients.

Management

The patients were classified into three groups retrospectively on the basis of management. The largest group, 16 patients, was treated surgically with ventricular outflow myotomy or myectomy. The second group, 7 patients, received propranolol and the third group, 13 patients, received no therapy. The groups were not matched for age or sex, and the hemodynamics and functional classification of the three groups (Table V) revealed a higher left ventricular gradient and a higher percentage of symptomatic patients in the surgical group. There was no significant difference in left ventricular end-diastolic pressure among patients in the three groups.

Surgical group: Of the 16 surgically treated patients, 12 male and 4 female, ranging in age from 8 months to 20 years, 13 had resection of the left ventricular outflow tract, 2 had resection of the right ventricular outflow tract, and 1 had combined resection of the right and left ventricular outflow tracts. The respective ages of the three youngest patients operated on were 8, 16 and 21 months. The operative mortality rate (death within 30 days of operation) was 6.3 percent (1 of 16 patients) (Table VI). The death occurred in an 8 month old boy who had severe congestive cardiac failure and was operated on in 1966. He underwent right ventricular outflow tract resection after cardiac catheterization, which had demonstrated that the pressure in the right ventricle was almost twice the systemic pressure. Autopsy revealed the features of idiopathic hypertrophic subaortic stenosis, previously undiagnosed, with severe septal hypertrophy involving the right ventricle. No other operative deaths have occurred.

Postoperative complications included a left ventricular aneurysm that was successfully resected in one patient.[15] Another patient had complete heart block that required the insertion of a permanent pacemaker. This patient has been followed up for 8.5 years and has remained asymptomatic. Three patients died suddenly in the late postoperative follow-up period (1.6, 2 and 10 years) after left ventricular outflow tract resection. Of the 12 long-term survivors, followed up for an average of 6.2 years (range 1.2 to 15.8), 7 are completely asymptomatic, and the other 5 have mild symptoms of dyspnea and infrequent chest discomfort related to severe exertion. One patient had supraventricular tachyarrhythmia 3 years postoperatively and has been receiving propranolol therapy for the last 9 years. The patient most recently operated on has received prophylactic propranolol therapy for 1.2 years.

Propranolol group: Seven patients (all male, aged 12 to 20 years) received propranolol therapy in an average dose of 120 mg/day (range 80 to 300). The three asymptomatic patients remained asymptomatic; three of the four patients with mild symptoms continued to have mild symptoms, and one patient's condition improved. No patient's condition deteriorated, and none of the patients died (Table VI). Propranolol was well tolerated by all seven patients.

Observation group: Thirteen patients (eight male and five female, aged 9 months to19 years) received no therapy (Table VI). Seven of these (54 percent) died. One patient, who was not suspected of having the disease and was followed up for 4.8 years with a diagnosis of mitral regurgitation, died with severe congestive cardiac failure; autopsy revealed typical features of idiopathic hypertrophic subaortic stenosis. Six patients (Table VII) followed up for a mean of 3.8 years died suddenly during normal activity; most had mild symptoms, and only one had normal left ventricular end-diastolic pressure.

Of the six survivors, followed up for an average of 6.8 years, four have remained asymptomatic, and the conditions of the other two have deteriorated. One patient

experiences mild dyspnea on exertion, and the other, who has a preexcitation syndrome, requires digoxin and quinidine for the control of arrhythmias.

Discussion

The cases described in this report span the entire era during which idiopathic hypertrophic subaortic stenosis has been recognized as a clinical entity. During this time the clinical presentation of this disease has ranged from asymptomatic to severely symptomatic. In some patients the disease is progressive, with increasing symptoms and disability, and sudden death can occur at any stage of the disorder.[13,16–19]

Slightly more than one third (13) of our 36 patients were asymptomatic and were initially evaluated because of a systolic murmur, which was present in all 36 patients. The remaining 23 patients presented with a spectrum of symptoms ranging from easy fatigability to severe congestive heart failure. The majority of patients were initially thought to have aortic valve stenosis, a ventricular septal defect or mitral insufficiency. In five patients (14 percent) a murmur had been documented at birth, and all five had right heart involvement. In 18 others (50 percent), the murmur had first been heard between the ages of 1 week and 5 years.

The association of congenital heart defects with idiopathic hypertrophic subaortic stenosis is well known.[20,21] In two of our patients, the idiopathic hypertrophic subaortic stenosis was detected only when a follow-up examination, after repair of coarctation of the aorta several years earlier, revealed the persistence of an apparently organic systolic murmur. Subsequent investigation led to the diagnosis of subaortic stenosis.

Clinical diagnosis: Our findings and those of previous studies suggest that the clinical diagnosis of idiopathic hypertrophic subaortic stenosis can be difficult in the young. In our series of patients, the diagnosis was suspected clinically in 11 patients (31 percent).

This diagnosis requires a high degree of alertness. A family history of heart murmur or sudden death in a relative with a heart murmur may be the first clue to the presence of the disease. Evaluation of the systolic murmur should include, when possible, Valsalva, postural and pharmacologic stimuli.[22] The electrocardiogram may be helpful, especially in patients who are asymptomatic or have a nonspecific murmur.

Echocardiography has proved an extremely useful noninvasive clinical aid in diagnosing idiopathic hypertrophic subaortic stenosis.[11,12,23] The finding of an asymmetrically thickened hypocontractile hypokinetic septum together with systolic anterior motion of the mitral valve is specific for the disease, and their presence in the asymptomatic young patient may make catheterization studies unnecessary.

Familial incidence: Previous reports[17,24] have indicated that the familial incidence rate of this disorder is 15 to 35 percent. However, if isolated echocardiographic asymmetric septal hypertrophy is considered evidence of the disease, the incidence may be much greater, because this abnormality is thought to be inherited as an autosomal dominant trait with variable penetrance.[25] However, isolated asymmetric septal hypertrophy has recently been reported in normal children, in children with various cardiac lesions and in patients with pulmonary hypertension.[26,27] Three patients (8 percent) in our study group had a family history of confirmed idiopathic hypertrophic subaortic stenosis, but the true familial incidence in our patients cannot be identified because only a few families underwent physical examination and echocardiography. Two of these three patients, one male and one female, died suddenly.

Association with lentiginosis: The association of multiple lentigines with an obstructive cardiomyopathy (Polani-Moynahan syndrome) has been well described,[28] but the nature of the cardiac abnormality has become clear only relatively recently. Somerville and Bonham-Carter[29] described three patients with lentiginosis who had severe right heart involvement and were initially thought to have pulmonary stenosis. Subsequently they were found to have idiopathic hypertrophic subaortic stenosis involving both ventricles. Of our four patients with lentiginosis, one had right heart involvement in addition to left heart involvement; another had an aortic coarctation resected 7 years before the diagnosis of idiopathic hypertrophic subaortic stenosis.

Mortality: Eleven (31 percent) of our 36 patients died; 9 (25 percent) died suddenly, including 3 who had had surgical treatment. The age at death ranged from 5 months to 26 years (mean 13 years). The average follow-up period was 4.8 years, with an annual mortality rate of 6 percent. These figures are similar to those recently reported[16] and reflect the seriousness of this disorder in the young.

Medical treatment: The definitive management of this disease in young patients is not clear, but the large mortality in our patients who received no therapy (7 of 13 patients) suggests that all patients should receive some form of treatment. Since its introduction, the beta adrenergic blocking drug propranolol has been shown to ameliorate the intensification of the pressure gradient during exercise in this disorder while producing little or no change in hemodynamic status at rest.[30,31] Symptoms, particularly dyspnea and angina, have decreased in some patients. Nevertheless, propranolol, like surgery, has not prevented sudden death.[16,18,19]

All of our propranolol-treated patients remained in stable condition or showed relief of symptoms, and to date none has required surgical intervention or died. These gratifying results are somewhat biased by the fact that the patients had milder symptoms, a lesser pressure gradient and a shorter follow-up period than those in the surgical group.

Surgical treatment: The role of surgical intervention remains the most controversial aspect of management of patients with idiopathic hypertrophic subaortic stenosis.[34] Despite the good relief of symptoms obtained in some patients in our study (Table VI) and in several other studies,[35,36] surgery did not abolish the risk of

sudden death. A multicenter study[37] has demonstrated that surgical therapy has no long-term advantage over medical therapy.

We currently recommend continuous propranolol therapy, even after surgical therapy, in all young patients with this disorder. The dose of propranolol ranges from 2.0 to 4.0 mg/kg body weight per day. We recommend surgery initially in patients who present with severe left ventricular outflow obstruction (basal pressure gradient of 80 mm Hg or more) with or without symptoms. We also recommend surgery in patients who continue to have or first experience angina, dyspnea or syncope while taking propranolol in adequate doses. The operation involves a wide resection of muscle from the hypertrophic ventricular outflow tract, currently using a transaortic approach. Because of the risk of infective endocarditis,[38] antibiotic prophylaxis should be used in all patients whether or not they are treated surgically. We also recommend that the patient avoid competitive sports and severe exertion because syncope and sudden death have been noted in association with these activities.

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Truncal or Aortic Valve Stenosis in Functionally Single Arterial Trunk

A Clinical, Hemodynamic and Pathologic Study of Six Cases

AMAN G. PATEL, MBBS, MRCP (UK), DCH (Lond)
OBERT M. FREEDOM, MD, FRCP (C), FACC
ENNETH R. BLOOM, MD, FRCP (C), FACC
ICHARD D. ROWE, MD, FRCP (Edin)

oronto, Ontario, Canada

Stenosis of the semilunar valve in the presence of a functionally single arterial trunk is uncommon. Three patients with truncus arteriosus, two with tetralogy of Fallot and pulmonary atresia and one with pulmonary atresia and intact septum were diagnosed as having stenosis of the truncal or aortic valve on the basis of clinical, echocardiographic, hemodynamic and angiocardiographic findings. Echocardiograms consistently showed multiple diastolic closure lines and abnormal semilunar valves in addition to the aortic override in five patients and hypoplastic right ventricle in the patient with pulmonary atresia and intact septum. Peak systolic gradients between the left ventricle and truncus (or aorta) at cardiac catheterization ranged from 20 to 47 mm Hg. Retrograde aortography confirmed a domed and stenotic semilunar valve. Cyanosis was progressive in the three patients with pulmonary atresia. Two patients had arterial anastomosis, and one had a right ventricle-pulmonary arterial graft in addition to aortic valvotomy. One of the three patients with truncus arteriosus underwent complete repair in addition to truncal valvotomy but he died in the post-operative period. The other two patients with truncus arteriosus died of intractable congestive cardiac failure before surgical intervention.

It is suggested that the presence of semilunar valve stenosis in these patients adversely affects the prognosis. The myocardium is already jeopardized as a result of hypoxia in pulmonary atresia and left ventricular diastolic overload in patients with truncus arteriosus. The added burden of semilunar valve stenosis may further compromise the functional status of the myocardium.

Although abnormalities of the semilunar valve in persistent truncus arteriosus were first described by Motta in 1932,[1] and subsequently by Roos in 1935,[2] little attention was paid to the morphologic variation of the truncal valve until recently. These abnormalities of the truncal valve usually lead to various degrees of truncal insufficiency,[3–7] and it is uncommon to document hemodynamically significant stenosis of the semilunar valve in truncus arteriosus. Significant truncal valve stenosis has been fully documented in only 10 patients,[8–11] although the true incidence of truncal valve stenosis is certainly greater.[12] Even less common is congenital stenosis of the aortic valve among patients with tetralogy of Fallot and pulmonary atresia or pulmonary atresia with intact ventricular septum. Because the arterial supply to the hypoplastic pulmonary arteries in pulmonary atresia is dependent on the patent ductus arteriosus or systemic collateral vessels from the aorta, the hemodynamic effects of semilunar valve stenosis would be similar to those in truncus arteriosus.

We report here the clinical, hemodynamic, angiocardiographic and pathologic findings in six patients with a functionally single arterial trunk

rom the Division of Cardiology, Departments f Paediatrics and Pathology, The Hospital for Sick hildren, and the Departments of Paediatrics and athology, The University of Toronto, Toronto, ntario, Canada. Manuscript received March 28, 978; revised manuscript received May 30, 1978, ccepted May 31, 1978.

Address for reprints: Robert M. Freedom, MD, he Hospital for Sick Children, 555 University venue, Toronto, Ontario, Canada M5G 1X8.

TABLE I

Summary of Cases

Case no.	Diagnosis	Age at Cath	Weight (kg)	LV/AO Gradient (mm Hg)	O_2 Sat in Truncus or Aorta (%)	Age at OP	Operative Procedure	Outcome
1	Tetralogy and pulmonary atresia	3 days	2.46	26	69	4 days	RV to MPA graft; aortic valvotomy	Died*
2	Tetralogy and pulmonary atresia	1 day	2.53	20	72	1 day	Waterston shunt	Alive
3	Truncus arteriosus (type II)	1 day	3.3	35	62	. . .	. . .	Died*
4	Truncus arteriosus (type I)	(a) 6 days	3.2	40	84	. . .	. . .	. . .
		(b) 2 yr	8.4	50	86	2 yr	Complete repair and truncal valvotomy	Died*
5	Truncus arteriosus (type II)	1 day	3.56	47	91	. . .	. . .	Died*
6	Pulmonary atresia with intact septum	(a) 2 days	2.8	. . .	63	3 days	Pulmonary valvotomy and Pott's anastomosis	Alive
		(b) 8 mo	7.2	27	79	. . .	. . .	. . .

* Necropsy examination performed in Cases 1, 3, 4 and 5.
AO = aorta; Cath = catheterization; LV = left ventricle; MPA = main pulmonary artery; OP = operation; RV = right ventricle; Sat = saturation.

and stenosis of the semilunar valve although we are cognizant of the embryologic, morphologic and clinical differences among the various types of patients with this diagnosis.

Case Material

Six patients—three with truncus arteriosus, two with tetralogy of Fallot and pulmonary atresia and one patient with pulmonary atresia and intact ventricular septum—form the basis of this report (Table I). All patients had a complete physical examination, 14 lead electrocardiogram, chest radiograph, M mode echocardiogram and complete cardiac catheterization and angiocardiographic investigations. Postmortem material was available for review in four patients (Cases 1 and 3 to 5).

Results

Clinical Features

No infant had a family history of congenital heart disease. The pregnancy and delivery had been uneventful in all cases, although a cardiac murmur was heard in one infant (Case 3) before birth. The distri-

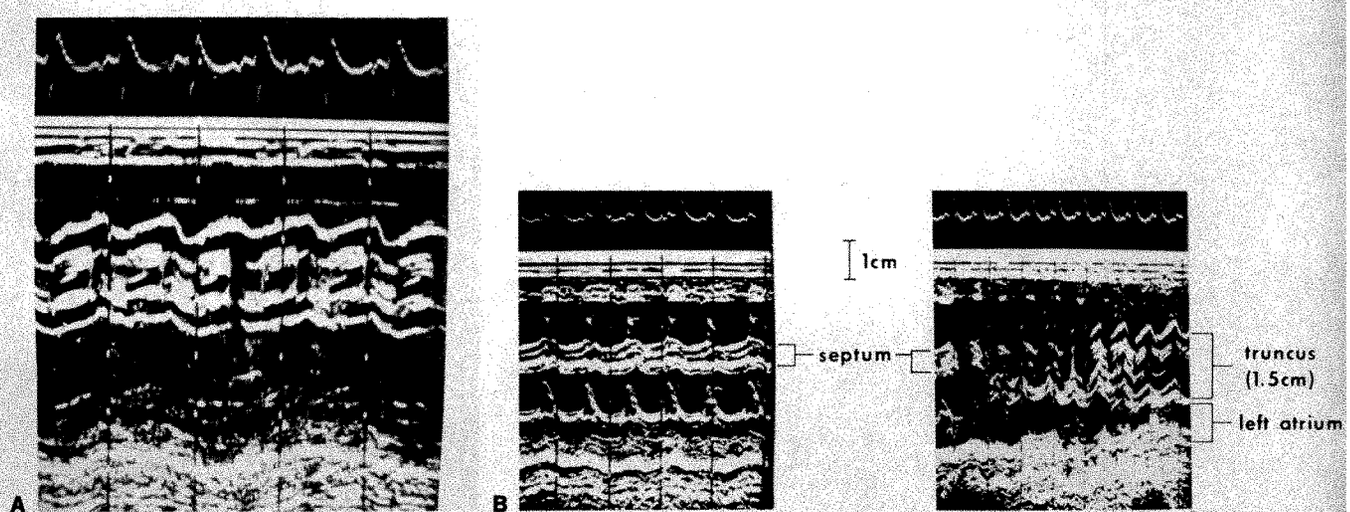


FIGURE 1. Case 5. Echocardiograms. **A,** showing a single arterial trunk (truncus) with multiple diastolic layering suggestive of a stenotic semilunar valve. **B,** showing biventricular enlargement **(left);** the scan from the ventricle to the truncal root **(right)** demonstrates the truncus overriding the ventricular septum (see Fig. 4).

ution of the infants' age and weight at the time of the nitial cardiac catheterization are presented in Table .

Physical findings: Cyanosis was present in three atients (Cases 1, 2 and 6). All but one infant (Case 6) had signs of marked congestive heart failure. A grade 2-3/6 systolic ejection murmur was audible at the left sternal edge in all, but the patient with pulmonary atresia and intact septum had a loud continuous murmur. An early diastolic murmur of truncal insufficiency

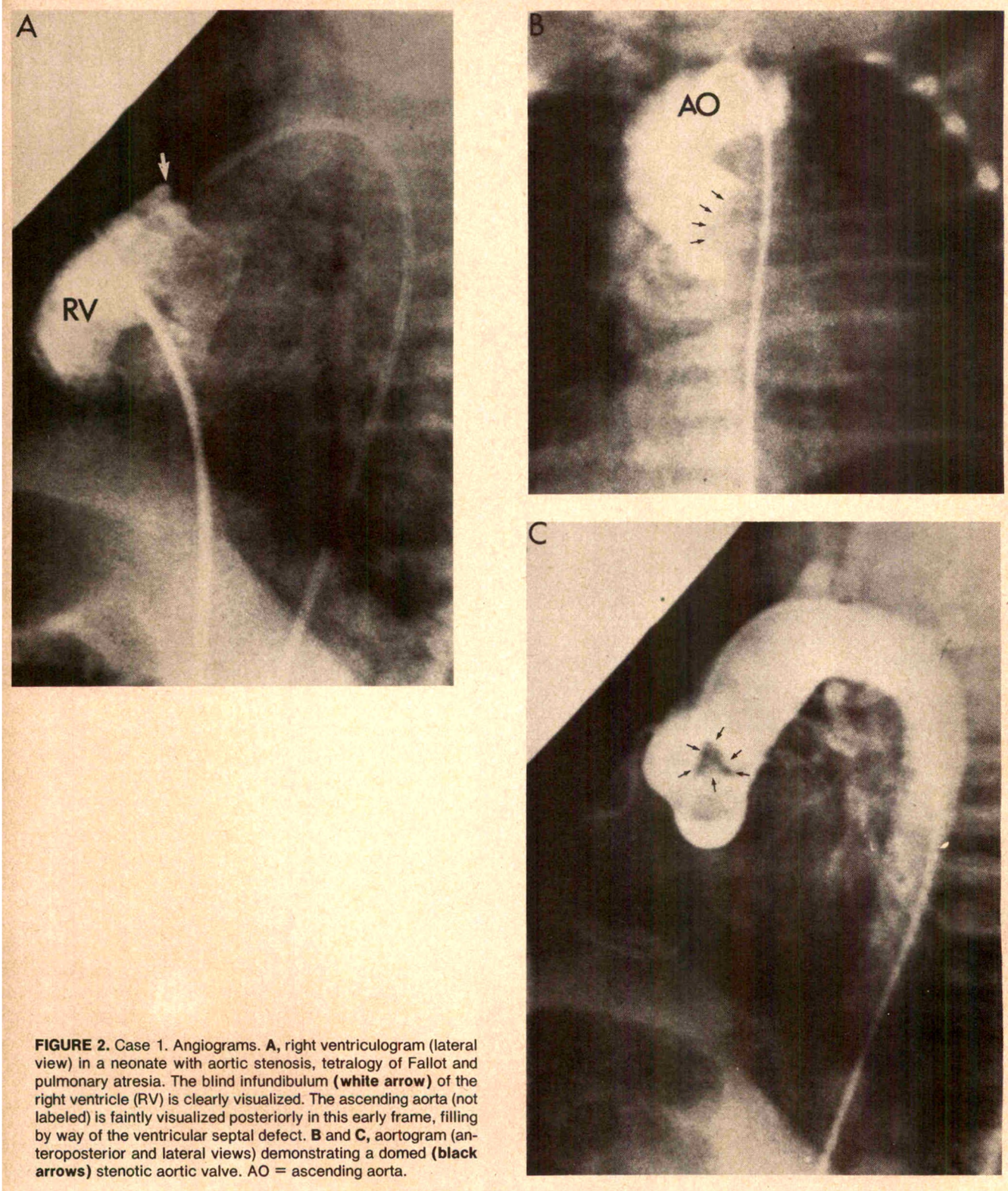


FIGURE 2. Case 1. Angiograms. **A,** right ventriculogram (lateral view) in a neonate with aortic stenosis, tetralogy of Fallot and pulmonary atresia. The blind infundibulum **(white arrow)** of the right ventricle (RV) is clearly visualized. The ascending aorta (not labeled) is faintly visualized posteriorly in this early frame, filling by way of the ventricular septal defect. **B** and **C,** aortogram (anteroposterior and lateral views) demonstrating a domed **(black arrows)** stenotic aortic valve. AO = ascending aorta.

was heard in Case 5 and a rumbling mid-diastolic murmur was present in Case 0, with type II truncus arteriosus. The second heart sound was single in all.

Electrocardiograms: These revealed sinus rhythm and a normal P-R interval in all. Right atrial enlargement was present in three (Cases 4 to 6). The mean QRS frontal axis was between +50° and +130°. Pure right ventricular hypertrophy was present in two infants (Cases 2 and 5) and combined ventricular hypertrophy in Cases 1, 3 and 4; marked left ventricular hypertrophy was found in Case 6. Repolarization changes consisting of S-T depression were present in anterolateral leads in three infants (Cases 2, 3 and 6), but T wave inversion was seen in Case 6 only.

Chest radiographs: These consistently showed cardiomegaly with a cardiothoracic ratio ranging from 0.6 to 0.8. The cardiac contour was normal except in two infants (Cases 3 and 4) who had a prominent pulmonary arterial segment. Lung vascularity was normal in one infant (Case 2), reduced in two infants (Cases 1 and 6) and increased in the remaining three. Pulmonary edema was present in two infants (Cases 1 and 6).

Echocardiograms: In Cases 1 and 2 the ultrasonic studies showed a large single root overriding the septum. The right ventricle was thick-walled but of normal size, as were the left ventricle and left atrium. There was mitral-aortic continuity. The aortic valve leaflets showed eccentric closure and multiple diastolic layering.

In Cases 3 to 5 there was biventricular enlargement, and the left atrium also appeared large. Again, a large single root overriding the septum was shown to have thickened abnormal leaflets with eccentric closure and multiple diastolic layering (Fig. 1). Left ventricular function was poor in all patients who died (ejection fraction 35 percent or less) (Fig. 1A).

Ultrasonic examination of Patient 6 (Table I) demonstrated a small right ventricle and tricuspid valve. The posterior root was in continuity with the mitral valve, but the leaflets of this root (presumably aortic) showed marked eccentricity.

Cardiac catheterization and angiocardiography: These procedures were performed by way of the right femoral vein and either the umbilical or the femoral artery. Hemodynamic data are presented in Table I. Simultaneous left ventricular and aortic pressures were obtained in five patients, but it was not possible to enter the left ventricle in one, and simultaneous right ventricular and aortic pressures were then recorded (Case 6, pulmonary atresia with intact septum). However, it was possible to record a gradient between the left ventricle and aorta in a subsequent study (Table I). The systolic gradient ranged from 20 to 47 mm Hg in the six cases. The relatively low systolic gradient may be explained by the presence of severe congestive cardiac failure and low cardiac output, as seen in aortic stenosis in infants. The oxygen saturation in the solitary arterial trunk varied from 63 to 91 percent (partial pressure of oxygen 28 to 54 mm Hg).

Selective angiocardiograms were performed using Hypaque® of 75 percent (1.5 ml/kg body weight) for each angiocardiogram. The angiocardiographic diagnoses are presented in Table I. The right ventricular angiocardiogram in Case 1 clearly demonstrated a blind infundibulum (Fig. 2A), and the ascending aorta filled by way of a ventricular septal defect. The aortogram demonstrated a stenotic aortic valve (Fig. 2, B and C). Similarly, in Case 2 with pulmonary atresia and ventricular septal defect, the blind right ventricular outflow tract was visualized. A narrow jet of contrast material into the ascending aorta was seen in the left ventriculogram (Fig. 3A). Pulmonary arterial branches in both of these cases were extremely hypoplastic and filled by way of a patent ductus arteriosus (Fig. 3, B and C). Retrograde aortograms in the three patients with a stenotic truncal valve showed an extremely dilated ascending portion of the truncus (Fig. 4) in comparison with findings in type I truncus without significant stenosis (Fig. 5). The coronary arterial distribution was normal. The typical angiographic appearances of the stenotic truncal valve and the truncus in Case 5 are shown in Figure 4.

The right ventriculogram in the patient with pulmonary atresia and intact septum (Case 6) showed a hypoplastic right ventricle with marked tricuspid incompetence (Fig. 6A). The retrograde aortogram clearly demonstrated the doming of the stenotic aortic valve. Pulmonary arterial branches filled by way of a patent ductus arteriosus (Fig. 6B).

Treatment: Cyanosis was progressive in three infants, and prostaglandin infusion[13] was required to maintain an adequate arterial oxygen tension (30 mm Hg) in Patients 1, 2 and 6, in whom ductal patency was maintained. Anastomotic procedures were required in all three infants and aortic valvotomy was attempted in Case 1. One patient (Case 4) showed initial improvement with digoxin and diuretic drugs but subsequently failed to thrive; he died at age 2 years, 2 days after repair of the truncus arteriosus.[14] Two other infants (Cases 3 and 5) presented with intractable congestive heart failure and low cardiac output with type II truncus arteriosus; both died within 48 hours after cardiac catheterization without the benefit of operation. These four deaths (Cases 1 and 3 to 5) form the basis of our pathologic material.

Postmortem Findings

Postmortem specimens were available for review for the three patients with truncus arteriosus and truncal valve stenosis (Cases 3 to 5) and one patient with tetralogy of Fallot, pulmonary atresia and aortic valve stenosis (Case 1).

Truncus arteriosus and truncal valve stenosis: Type II truncus arteriosus was identified in two patients and type I in one patient; all three patients had cardiomegaly. The three specimens exhibited levocardia, atrial situs solitus, concordant atrioventricular (A-V) connections and fibrous continuity between the anterior mitral leaflet and truncal valve. No abnormalities of systemic or pulmonary venous return were observed. The foramen ovale was patent in all cases. In the patient with type I truncus arteriosus, complete repair had been

attempted using an external valved conduit to provide continuity between the right ventricle and pulmonary artery, patch closure of the ventricular septal defect and valvotomy of the truncal valve. The three hearts studied had right and left A-V valves with the morphologic features of the normal tricuspid and mitral valves, respectively.

A ventricular septal defect was evident in three patients, located in the superoanterior portion of the ventricular septum, with the truncal valve as the roof of the ventricular septal defect (Fig. 7 and 8). The infundibular or conal septum was absent in the three cases, and the defect appeared relatively small in one case and typical of truncus arteriosus in the others.

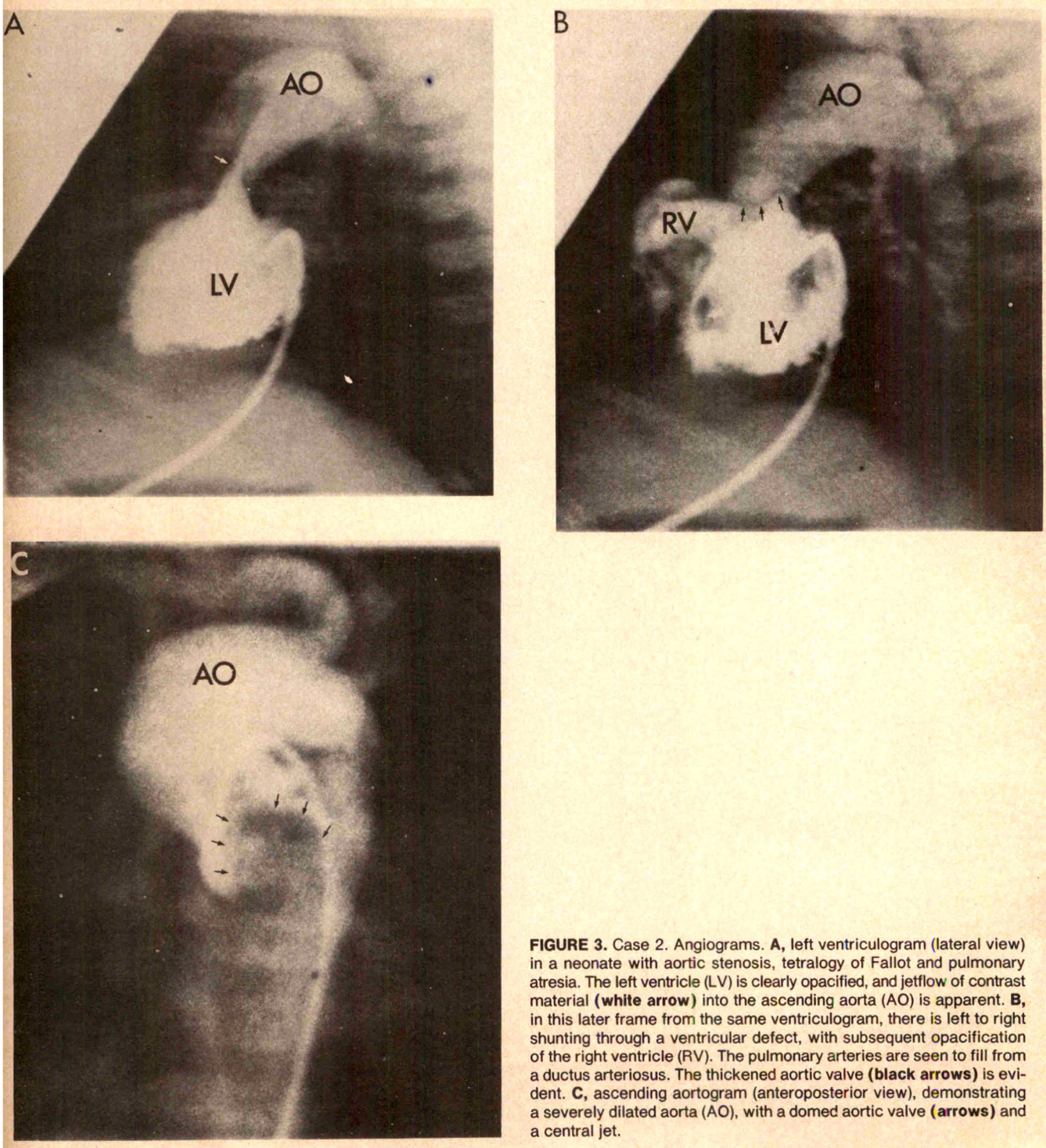
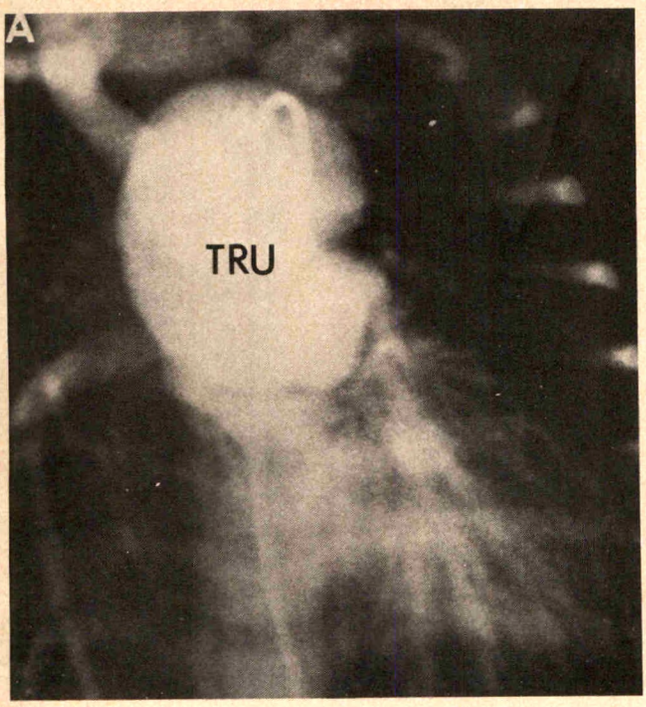


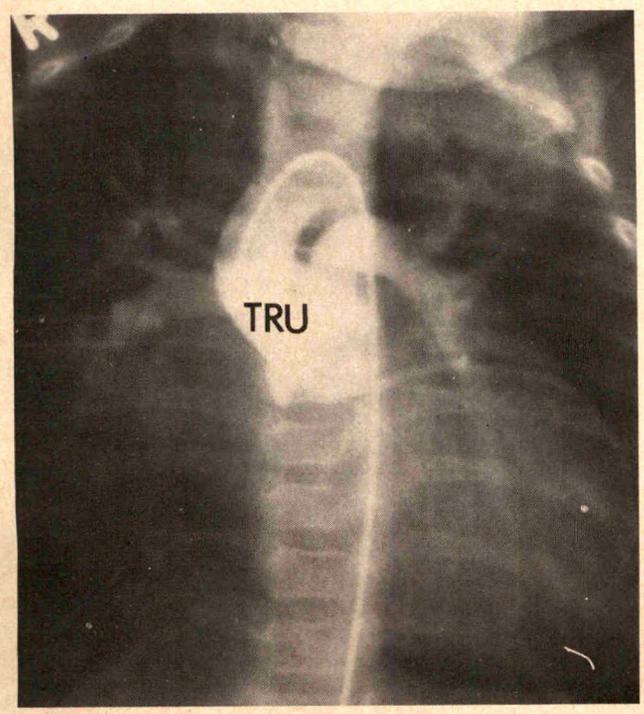
FIGURE 3. Case 2. Angiograms. **A,** left ventriculogram (lateral view) in a neonate with aortic stenosis, tetralogy of Fallot and pulmonary atresia. The left ventricle (LV) is clearly opacified, and jetflow of contrast material **(white arrow)** into the ascending aorta (AO) is apparent. **B,** in this later frame from the same ventriculogram, there is left to right shunting through a ventricular defect, with subsequent opacification of the right ventricle (RV). The pulmonary arteries are seen to fill from a ductus arteriosus. The thickened aortic valve **(black arrows)** is evident. **C,** ascending aortogram (anteroposterior view), demonstrating a severely dilated aorta (AO), with a domed aortic valve **(arrows)** and a central jet.

There was no continuity between the tricuspid and truncal valve. The trabecula septomarginalis was well formed in the three patients.

The truncal valve was quadricuspid in two and tricuspid in one. The free valve margins were thickened, polypoid and myxomatous (Fig. 9). Prolapse of the truncal valve was not present. The ascending portion of the truncus was extremely dilated in one case (Case 5). The aortic arch was left-sided in two, and in one there was a right cervical aortic arch with mirror-image origin of the brachiocephalic vessels. The coronary arterial origin and distribution were normal in all three cases. Both ventricles were uniformly hypertrophied.

The parathyroid and thymus glands were absent in





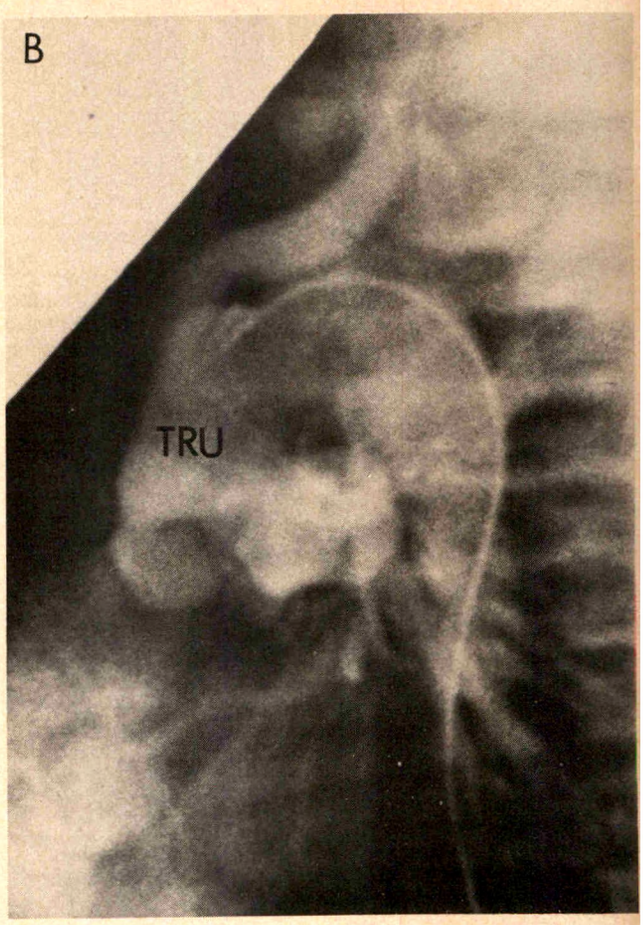
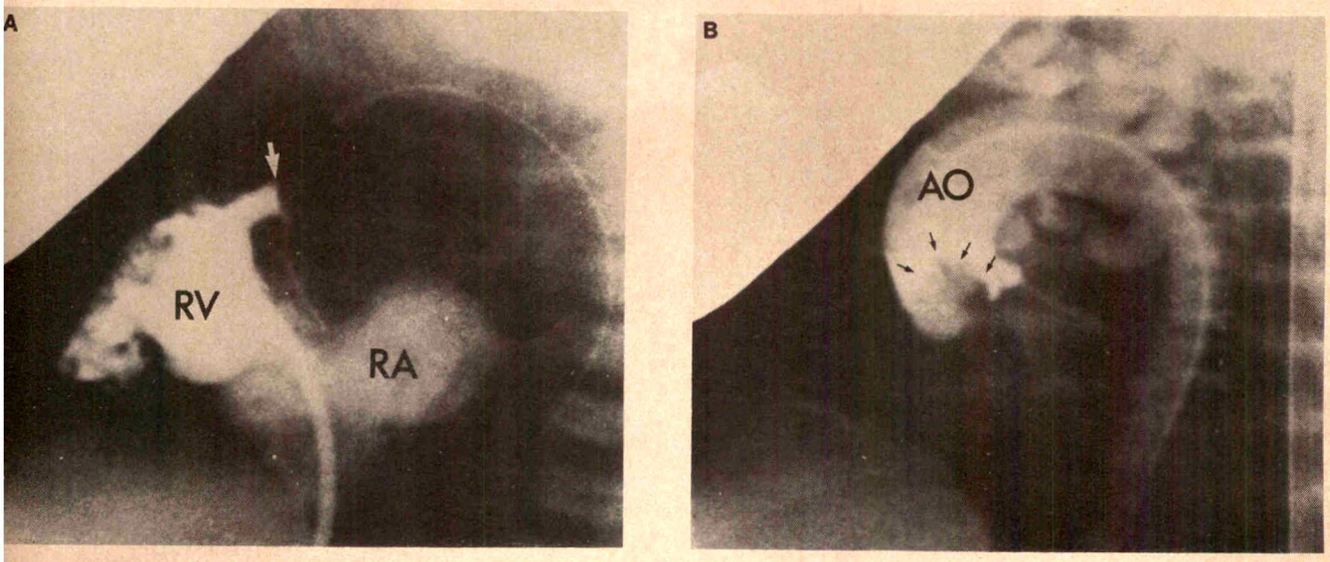


FIGURE 4 (above). Case 5. Retrograde anteroposterior **(A)** and lateral **(B)** angiographic study in a 1 day old infant with severe truncal valve stenosis. **A,** the ascending portion of the truncus (TRU) is severely dilated. The origin of the pulmonary arteries is not readily apparent (type II truncus arteriosus was found at autopsy). **B,** lateral projection, demonstrating the greatly dilated truncus and the disorganized truncal valve.

FIGURE 5 (left). Retrograde arterial angiogram in a newborn with type I truncus arteriosus. The ascending portion of the truncus (TRU) is only mildly dilated, and the truncal valve was neither regurgitant nor stenotic (compare with Fig. 4).



IGURE 6. Case 6. A neonate with pulmonary atresia and intact ventricular septum **A,** lateral right ventriculogram. In this projection, the right ventricle RV) appears only mildly hypoplastic. The pulmonary valve **(white arrow)** is atretic. There is significant tricuspid regurgitation into a dilated right trium (RA). **B,** retrograde aortogram in lateral projection obtained using an umbilical arterial cannula. The aorta (AO) is dilated, and the stenotic ortic valve is clearly domed **(arrows).** A ductus arteriosus is evident.

ne patient who was thought to have the DiGeorge yndrome.

Tetralogy of Fallot with pulmonary atresia: The eart and lungs were available for study in one infant ith tetralogy, pulmonary atresia and aortic valve ste- osis (Case 1). This infant, who had extremely under- eveloped pulmonary arteries, underwent unsuccessful alliative surgery, consisting of construction of a conduit rom the right ventricle to the pulmonary artery and ortic valvotomy. The ventricular septal defect was left pen.

Cardiovascular examination in this patient showed evocardia, visceroatrial situs solitus, concordant A-V onnections and a patent conduit from the right ventricle to the confluence of the right and left pulmonary arteries. These branches had measured 2.0 and 3.0 mm, respectively. There were no abnormalities of the systemic or pulmonary venous return. The tricuspid and mitral valves were normal. Aortic override of the ventricular septal defect was seen, but there was fibrous continuity between the anterior mitral leaflet and the aortic valve. The ventricular septal defect was similar to that observed in the patients with truncus arteriosus (Fig. 10). The floor of the defect and its anterior margin were formed by the trabecula septomarginalis. The posterior margin of the defect was fibrous and was closely related to the anterior leaflet of the tricuspid valve.

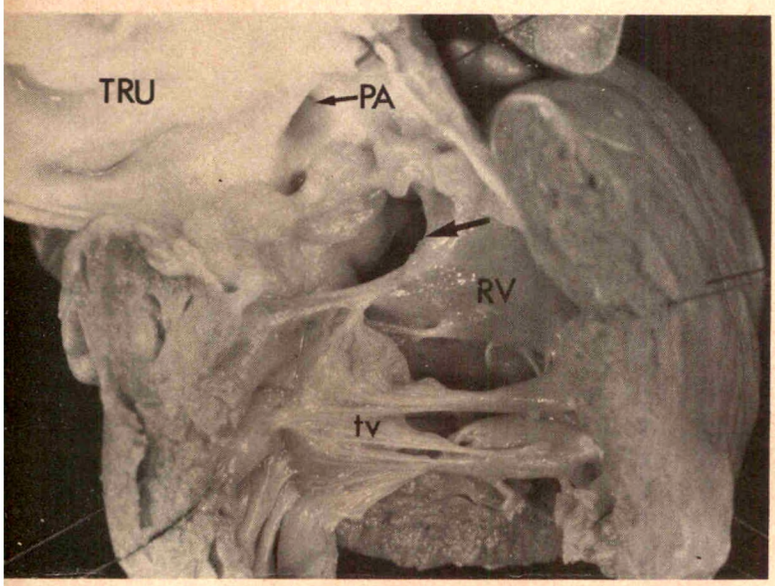


FIGURE 7. Case 5. Opened right ventricle (RV). The truncus (TRU) clearly overrides the ventricular defect **(large black arrow).** The tricuspid valve (tv) has its septal insertion nearly adjacent to the ventricular defect. The origin of one pulmonary artery (PA) is seen superior to the thickened fleshy truncal valve.

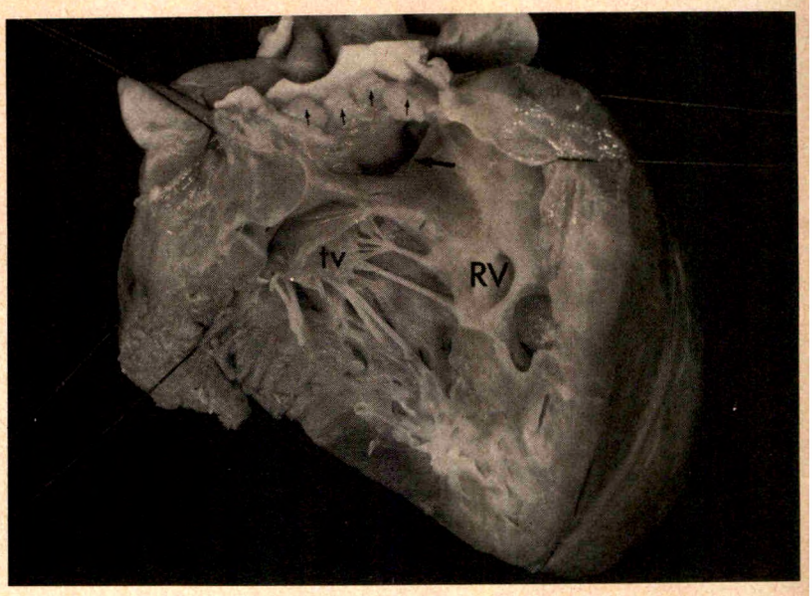


FIGURE 8. Case 3. Opened right ventricle (RV). There is a large truncal type ventricular septal defect **(large black arrow)** with the nodular stenotic truncal valve clearly evident **(small black arrows).** The tricuspid valve (tv) is not continuous with the truncal valve.

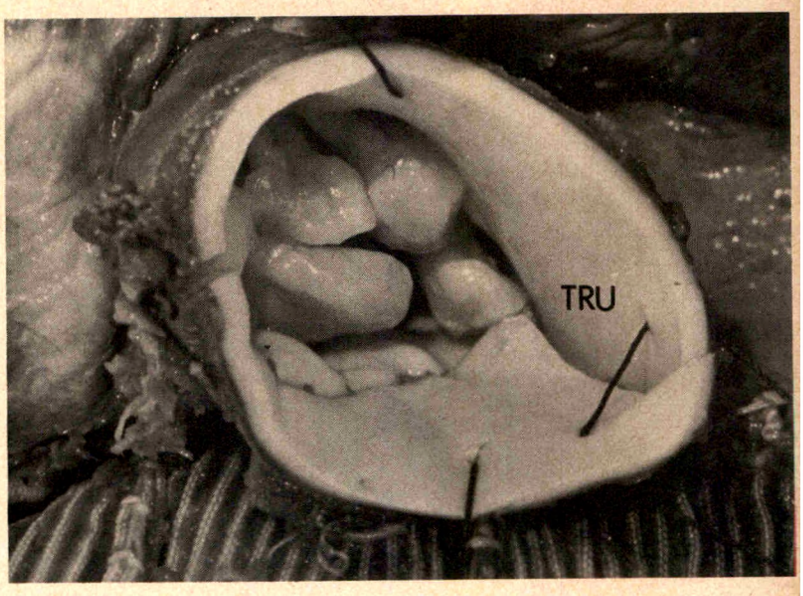


FIGURE 9. Case 4. Close-up view of quadricuspid fleshy redundant and stenotic truncal (TRU) valve.

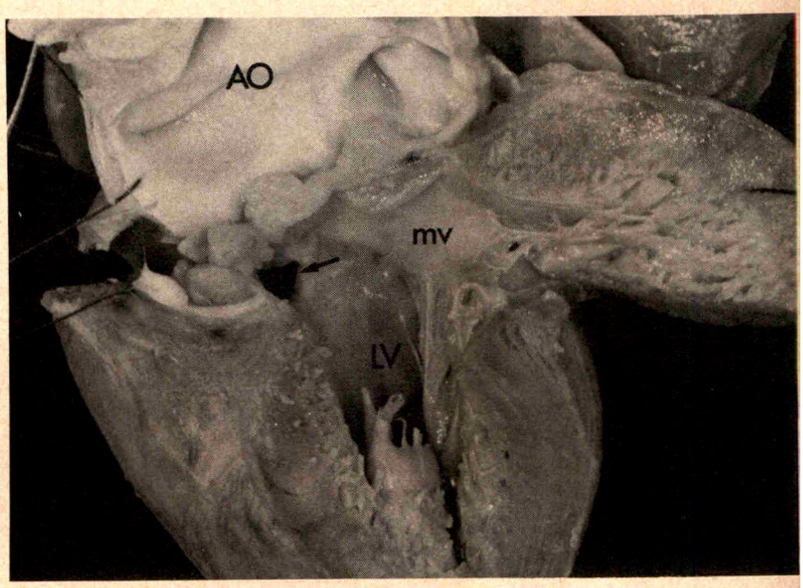


FIGURE 10. Case 1. Internal view of left ventricle (LV) in a neonate with aortic stenosis, tetralogy of Fallot and pulmonary atresia. The thickened stenotic aortic valve and dilated ascending aorta (AO) are clearly visible. Mitral valve (mv)-aortic valve fibrous continuity is present. The subaortic ventricular septal defect **(arrow)** is immediately beneath the right aortic leaflet. The left ventricular wall is hypertrophied.

The aortic valve was tricuspid and the commisures were fused. The valve was thickened and rigid, and the free margin was nodular and polypoid.

The aortic arch was left-sided, a left-sided narrowed ductus arteriosus supplying the left pulmonary artery. In addition, the right subclavian artery was the last brachiocephalic artery to originate from the aorta.

Finally, histologic examination of the myocardium from these four patients showed various degrees of subendocardial myocardial ischemia and fibrosis, with some myocytolysis.

Discussion

Regurgitation versus stenosis of truncal valve: Morphologic abnormalities of the truncal valve are not uncommon, and the gross and histopathologic features of these distorted valves have received adequate attention.[1–11,15] It is not surprising that these fleshy, redundant myxomatous valves do not function normally. Truncal valve regurgitation was reported in 12 of 79 (15 percent) autopsy cases by Calder et al.,[12] and truncal insufficiency was considered present in 2.2 percent (4 of 180) patients described by Bharati et al.[16] It is likely that the latter incidence rate underestimates the frequency of functional regurgitation of the truncal valve.

In our experience with 131 infants and children with truncus arteriosus, significant obstruction of the truncal valve is considerably less common than regurgitation. This seems to be the experience of other centers as well.[8–12] Among our three patients with truncal valve stenosis, the conal septal defect was small in one, and typical of the truncus arteriosus in two. Rosenquist et al.[5] have previously called attention to the variability in size of the conal defects in truncus arteriosus. There does not seem to be any relation between the size of the conal defect and the presence or absence of truncal valve stenosis.

Aortic valve abnormalities in tetralogy of Fallot and pulmonary atresia: Functionally significant abnormalities of the aortic valve are also uncommon in patients with tetralogy of Fallot and pulmonary atresia or with pulmonary atresia and intact septum. Certainly, there are similarities between truncus arteriosus and tetralogy with pulmonary atresia. The embryogenic and morphologic similarities have recently been reviewed.[17–19] In the study of Crupi et al.[17] 64 of 66 specimens of truncus arteriosus had some abnormality of the truncal valve. The incidence of structural abnormalities of the aortic valve among patients with tetralogy of Fallot with pulmonary atresia is certainly considerably smaller. Among patients with pulmonary atresia and intact septum, aortic stenosis is very rare.

Prognosis: Patients with significant truncal valve abnormalities often do not respond to intensive medical therapy and many die in early infancy. Gelband et al.[4] had no survivors in this group with severe truncal valve regurgitation. By contrast, truncal valve abnormalities in older infants and children do not seem to affect the prognosis to the same extent and thus, by inference, are probably mild.[20,21] Only one survivor has been reported among six patients with truncal valve stenosis.[11] The integrity of the myocardium in patients with truncus arteriosus is already jeopardized. The presence of a large volume overload, mild to moderate hypoxemia and a low diastolic coronary perfusion pressure may predispose the subendocardial myocardium of these patients to ischemia.[22] The added burden of semilunar valve stenosis may further compromise the functional and anatomic status of the myocardium, resulting in progressive congestive heart failure.[23] Similarly, aortic valve stenosis in patients with pulmonary atresia with intact ventricular septum and hypertensive right ventricle may further jeopardize adequate oxygenation of the vulnerable subendocardial myocardium. A significant number of these patients will already have myocardial sinusoidal-coronary arterial communications frequently involving the left anterior descending coronary artery.

Clinical recognition of truncal valve stenosis: Although stenosis of the semilunar valve in functionally single arterial trunk is uncommon, its clinical recognition is possible. Echocardiography is of great help in the initial clinical assessment of patients with this condition. The basic features of the underlying abnormalities were well defined in all of our cases. In addition, the multiple diastolic layering of the semilunar valve with marked eccentric closure was also seen.[24,25] This has not been a feature of our patients with truncus arteriosus with nonobstructed truncal valve even when the valve is quadricuspid. In addition, the patients with truncal stenosis in this group had greatly thickened leaflet echoes, a finding consistent with the polypoid and myxomatous structure of the valve. As is common in infants and children with semilunar valve stenosis,[26] the degree of leaflet separation in systole did not always reflect the severity of the stenosis.

Left ventricular function was considerably impaired in these patients, and such critically ill infants frequently do not tolerate angiocardiography. Thus, the echocardiogram can be utilized as an adjunct to cardiac catheterization and can help limit the number of angiograms and hence the dose of contrast agent used in these very sick infants. In our six patients retrograde aortography provided excellent visualization of the disturbed aortic or truncal root. Very few aortograms obtained from infants with stenotic truncal valves have been published, but certainly none have shown a larger or more distorted ascending aorta (truncus) than that observed in our patients with truncal valve stenosis. Finally, clinical recognition of systemic semilunar valve stenosis in infants with a functionally single arterial trunk is important because it may have specific implications in determining initial therapy.

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Estimation of Pulmonary/Systemic Resistance Ratios From Echocardiographic Systolic Time Intervals in Young Patients With Congenital or Acquired Heart Disease

ERIC W. SPOONER, MD
BURTON L. PERRY, MD
AARON M. STERN, MD
JOAN M. SIGMANN, MD

Ann Arbor, Michigan

Previous work has shown the positive correlation of echocardiographic right ventricular preejection period/right ventricular ejection time ratio (RPEP/RVET) with pulmonary vascular resistance and pulmonary arterial diastolic pressure obtained at cardiac catheterization. However, the correlation was insufficient to predict pulmonary arterial diastolic pressure or vascular resistance from a given RPEP/RVET ratio. In this study the RPEP/RVET ratio was compared with left ventricular preejection period/ejection time ratio (LVEP/LVET) in 25 patients undergoing cardiac catheterization, and a strong correlation was found between the ratio (RPEP/RVET)/(LPEP/LVET) = R/L and the ratio of pulmonary arteriolar resistance/systemic arteriolar resistance (PAR/RS), especially when R/L was correlated with $\log_{10}$ PAR/RS ($r = 0.902$). A very high correlation ($r = 0.960$) was found between R/L and $\log_{10}$ PAR/RS when the group was restricted to patients with a ventricular septal defect or a complete endocardial cushion defect. Regression equations for prediction of PAR/RS have been derived for the various groups.

Since its introduction to clinical use, echocardiography has been evolving from a qualitative descriptive tool of diagnosis to a procedure providing quantitative data. Pediatric and adult cardiologists alike are asking for quantitative measurements and estimates of various hemodynamic variables. Therefore, after the qualitative descriptions of pulmonary valve motion in pulmonary hypertension,[1,2] great interest was created by the quantitative correlation of right ventricular systolic time intervals with pulmonary arterial diastolic pressure and pulmonary vascular resistance reported by Hirschfeld et al.[3] However, although statistically significant, the correlation coefficients between right ventricular systolic time intervals and pulmonary arterial diastolic pressure or vascular resistance were inadequate to predict these values accurately.[4] Clearly, further investigation was needed to provide the data required for more accurate prediction. In this study we assessed whether one could more accurately predict the pulmonary vascular resistance/systemic vascular resistance ratio by comparing the patient's left and right ventricular systolic time intervals because the normal range of pulmonary/systemic vascular resistance ratio is well known.

Case Material

Thirty patients undergoing diagnostic cardiac catheterization at the University of Michigan Medical Center for delineation of congenital or acquired heart disease underwent echocardiography within 12 hours of the catheterization; in most cases the procedure was performed in the catheterization laboratory immediately before the hemodynamic study. Patients were not studied in the first 6 hours after catheterization. Patients with a complete right or left bundle branch block pattern in the electrocardiogram, complete transposition of the great ar-

From the Department of Pediatrics, Section of Pediatric Cardiology, University of Michigan Medical Center, Ann Arbor, Michigan. Manuscript received December 12, 1977; revised manuscript received June 6, 1978, accepted June 7, 1978.
Address for reprints: Eric W. Spooner, MD, Department of Pediatric Cardiology, Albany Medical Center Hospital, 47 New Scotland Avenue, Albany, New York 12208.

TABLE I

Summary of Echocardiographic and Cardiac Catheterization Data in 25 Cases

Case no.	Diagnosis	RPEP/RVET	LPEP/LVET	R/L	PAR	TPR	RS	PAR/RS	TPR/RS	Log_{10} PAR/RS	Log_{10} TPR/RS
1	VSD	0.187	0.301	0.621	1.27	2.89	12.55	0.101	0.230	−0.996	−0.638
2	VSD	0.637	0.557	1.133	35.7	38.1	14.9	2.35	2.56	0.371	0.408
3	ASD	0.203	0.422	0.481	0.766	1.72	16.67	0.046	0.103	−1.337	−0.987
4	VSD	0.192	0.340	0.565	0.972	2.92	22.06	0.044	0.132	−1.356	−0.879
5	ASD	0.186	0.283	0.657	1.43	1.94	24.14	0.059	0.080	−1.229	−1.095
6	Pulm emboli	0.595	0.691	0.861	10.39	14.34	32.62	0.319	0.440	−0.496	−0.357
7	PS	0.112	0.154	0.727	1.65	3.32	16.82	0.098	0.197	−1.009	−0.706
8	VSD, PDA	0.199	0.236	0.843	4.02	5.85	19.78	0.203	0.296	−0.693	−0.529
9	Normal	0.201	0.297	0.676	1.77	2.74	14.18	0.125	0.193	−0.903	−0.714
10	ECD	0.220	0.254	0.866	5.52	6.18	18.94	0.292	0.326	−0.535	−0.487
11	AS, PS	0.096	0.164	0.588	1.39	5.03	27.42	0.051	0.184	−1.294	−0.736
12	VSD	0.170	0.291	0.584	2.56	3.62	24.34	0.105	0.1486	−0.979	−0.828
13	ECD	0.189	0.233	0.850	8.60	9.21	33.18	0.259	0.278	−0.587	−0.556
14	Inf PS	0.189	0.324	0.582	1.09	2.36	11.81	0.092	0.200	−1.034	−0.699
15	ECD	0.327	0.295	1.108	3.02	3.42	3.25*	0.929	1.053	−0.032	0.022
16	ASD	0.194	0.318	0.612	1.14	1.77	19.94	0.057	0.089	−1.243	−1.052
17	PS	0.212	0.252	0.838	2.47	4.63	23.46	0.105	0.197	−0.979	−0.706
18	PDA	0.159	0.298	0.533	1.29	1.90	13.53	0.095	0.140	−1.021	−0.854
19	VSD	0.142	0.250	0.568	0.91	2.55	26.11	0.035	0.098	−1.456	−1.009
20	AS	0.264	0.350	0.753	2.08	6.24	27.01	0.077	0.231	−1.114	−0.636
21	VSD	0.229	0.271	0.842	7.00	10.67	23.29	0.301	0.458	−0.521	−0.339
22	a-v fist;	0.306	0.343	0.891	2.73	3.23	5.93	0.461	0.544	−0.337	−0.265
23	AS	0.263	0.330	0.798	1.70	4.16	17.20	0.099	0.242	−1.005	−0.616
24	ASD	0.172	0.280	0.615	0.83	1.53	25.12	0.033	0.061	−1.482	−1.215
25	VSD	0.174	0.303	0.575	1.51	2.45	17.34	0.087	0.141	−1.061	−0.851

* Hemoglobin 4.2 g/100 ml at time of echocardiography and cardiac catheterization.

PAR, TPR, RS are expressed in units of mm Hg/liter per min per m^2.

AS = aortic stenosis; ASD = atrial septal defect; a-v fist = cerebral arteriovenous fistula; ECD = endocardial cushion defect; Inf PS = infundibular pulmonary stenosis; PAR = pulmonary arteriolar resistance (mm Hg/liter per min per m^2); PDA = patent ductus arteriosus; PS = pulmonary stenosis; Pulm = pulmonary; RS = systemic resistance (mm Hg/liter per min per m^2); TPR = total pulmonary resistance (mm Hg/liter per min per m^2); VSD = ventricular septal defect.

teries or a cardiac pacemaker were specifically excluded from the study, as were patients breathing a greater than 40 percent oxygen concentration (only Patient 15, breathing 35 percent oxygen, was not in room air). Patients with an incomplete right bundle branch block pattern with a QRS interval within normal limits for age[5] were included. Of these 30 patients, 25 had echocardiographic and cardiac catheterization data suitable for inclusion. Their diagnoses are included in Table I. All patients were under 10 years of age except Patients 2 (18 years) and 6 (15 years).

Methods

Echocardiograms: These were obtained with 5.0, 3.5 or 2.25 megahertz nonfocused Aerotech transducers, and either a Picker model 104 ultrasonoscope with Polaroid® film recording or a Smith Kline model 20-A ultrasonoscope and Smith Kline model 21 fiberoptic strip chart recorder. Echocardiograms of the aortic and pulmonary valves were obtained with standard techniques and recorded so that one complete cardiac cycle was obtained per sweep on the Polaroid camera, or at a paper speed of 100 mm/sec on the Smith Kline instrument. Only complexes including both the opening and closing movements of the valve under study were included. The echocardiographic limb lead showing the earliest depolarization, usually lead II, was utilized and superimposed on the echocardiographic tracing. Measurements of preejection period and ejection period were made as previously described[3] (Fig. 1) with the additional technique of utilizing a dial caliper, accurate to ±0.05 mm, measuring the intervals to the nearest 0.1 mm and using a drafting triangle and stylus to make parallel rulings at the onset of the Q wave and the opening and closure of the valve in question. Measurements in millimeters were then converted to seconds (carried to three significant digits), using the highly accurate and stable interval time markers generated by each instrument. At least six cardiac cycles for each valve, during all phases of respiration, were measured and the values averaged. All measurements were carried out by one observer (E.S.).

Cardiac catheterization: This procedure was carried out with the patient under light morphine and diphenhydramine (Benadryl®) sedation, and samples for oxygen saturation and pressure measurements were obtained simultaneously or in rapid succession (less than 2 minutes) from the pulmonary artery, pulmonary vein, systemic artery and mixed venous return. When pulmonary venous return or pulmonary arterial wedge saturation could not be sampled (five cases) it was assumed to be the same as the systemic arterial or left ventricular saturation, provided there was no right to left shunting as shown with angiography or an arterial saturation level above 93 percent, or both. Samples were analyzed for oxygen saturation with an American Optical Corporation reflectance oximeter or Instrumentation Laboratories Company transmittance oximeter, or both. Values for assumed oxygen consumption were obtained from tables as reported by Cayler et al.[6] for infants, and LaFarge and Miettinen[7] for children over age 3 years. Pressures were obtained with no. 5, 6 and 7F National Institutes of Health or Cournand (USCI, Billerica, Massachusetts) or Gensini (Edwards Laboratories, Santa Ana, California) catheters of 50, 80 and 100 cm lengths coupled to Statham P23Db strain gauge transducers and recorded on an

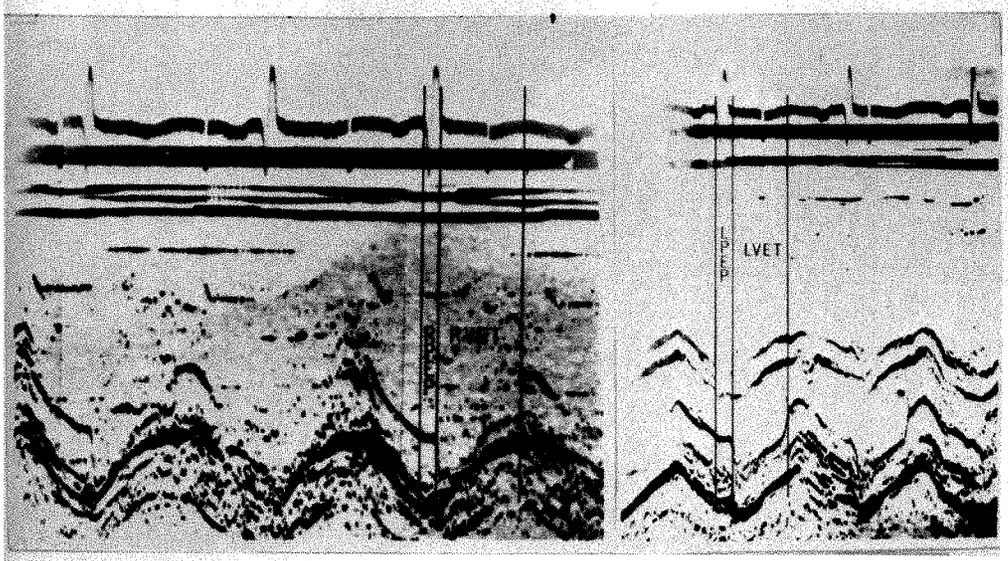


FIGURE 1. Patient 16. **Left,** echocardiographic tracing of pulmonary valve, showing method of measurement of right ventricular preejection period (RPEP) and ejection time (RVET). RPEP/RVET = 0.203 in this patient, whose pulmonary arteriolar resistance = 1.14 mm Hg/liter per min per m^2. **Right,** echocardiographic tracing of aortic valve, showing method of measurement of left ventricular preejection period (LPEP) and ejection time (LVET). LPEP/LVET in this instance = 0.315.

Electronics for Medicine VR6 photo-optical recorder. Catheterization values thus obtained were entered into a Digital Equipment Corporation PDP-12 computer programmed to calculate flows by standard Fick principle and to report pulmonary arteriolar, total pulmonary and systemic arteriolar resistances in units of mm Hg/liter per min per m^2 of body surface area. So as to preclude observer bias this analysis was performed after analysis of the echocardiographic systolic time intervals.

The resultant data points were entered into the University of Michigan Data Terminal System, and correlation matrices and linear regression analysis carried out by the method of least-squares using the MIDAS statistical research package.

Results

Table I lists the results of the echocardiographic systolic time intervals and cardiac catheterization data for the 25 patients. As might be expected, there was a

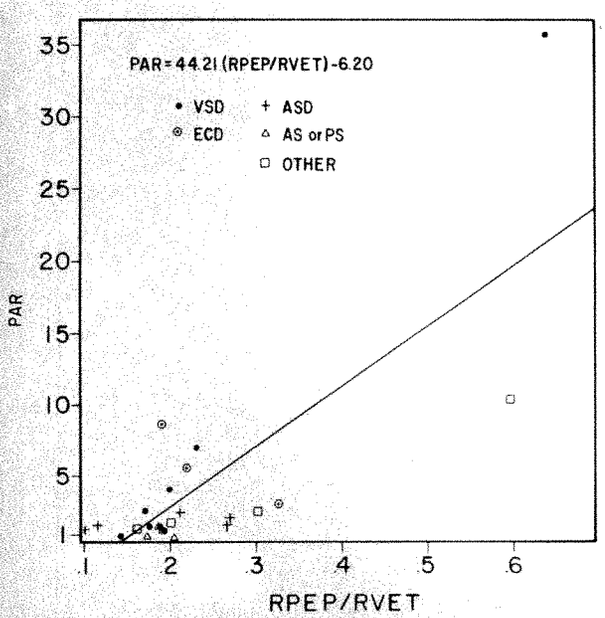


FIGURE 2. Right ventricular preejection period/right ventricular ejection time ratio (RPEP/RVET) in 25 patients is plotted against pulmonary arteriolar resistance (PAR) in units of mm Hg/liter per min per m^2 together with the regression line. Although there is a fair degree of scatter, the correlation coefficient (r) is 0.787, and the linear regression equation is PAR = 44.21 (RPEP/RVET) − 6.20. AS = aortic stenosis; ASD = atrial septal defect; ECD = endocardial cushion defect; PS = pulmonary stenosis; VSD = ventricular septal defect.

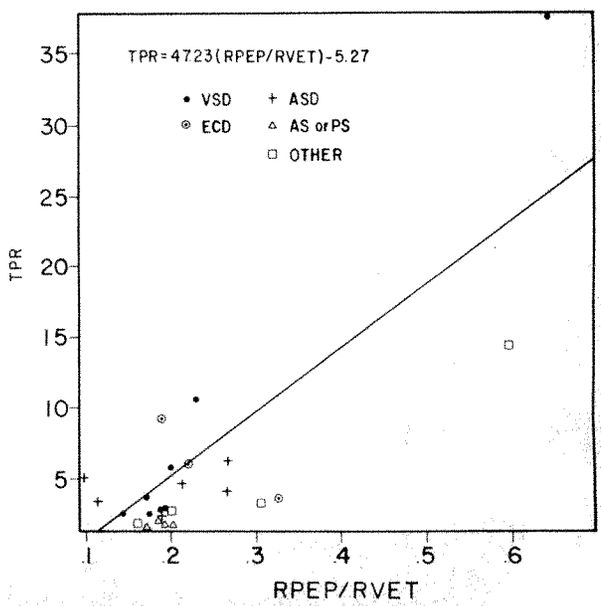


FIGURE 3. Right ventricular preejection period/right ventricular ejection time ratio (RPEP/RVET) in 25 patients is plotted against total pulmonary resistance (TPR) in units of mm Hg/liter per min per m^2, together with the regression line. Although there is a fair degree of scatter again, r = 0.800 and TPR = 47.23 (RPEP/RVET) − 5.27 by least-squares regression analysis. Abbreviations as in Figure 2.

preponderance of children with ventricular septal defect, atrial septal defect or endocardial cushion defect.

Right/left systolic interval ratios compared with pulmonary/systemic resistance ratios: The ratio of right ventricular preejection period/right ventricular ejection time (RPEP/RVET) was compared with pulmonary arteriolar resistance and total pulmonary resistance using linear regression analysis (Fig. 2 and 3). There was a significant statistical correlation between these values, with the correlation coefficient of 0.787 (r^2 = 0.619) for RPEP/RVET versus pulmonary arteriolar

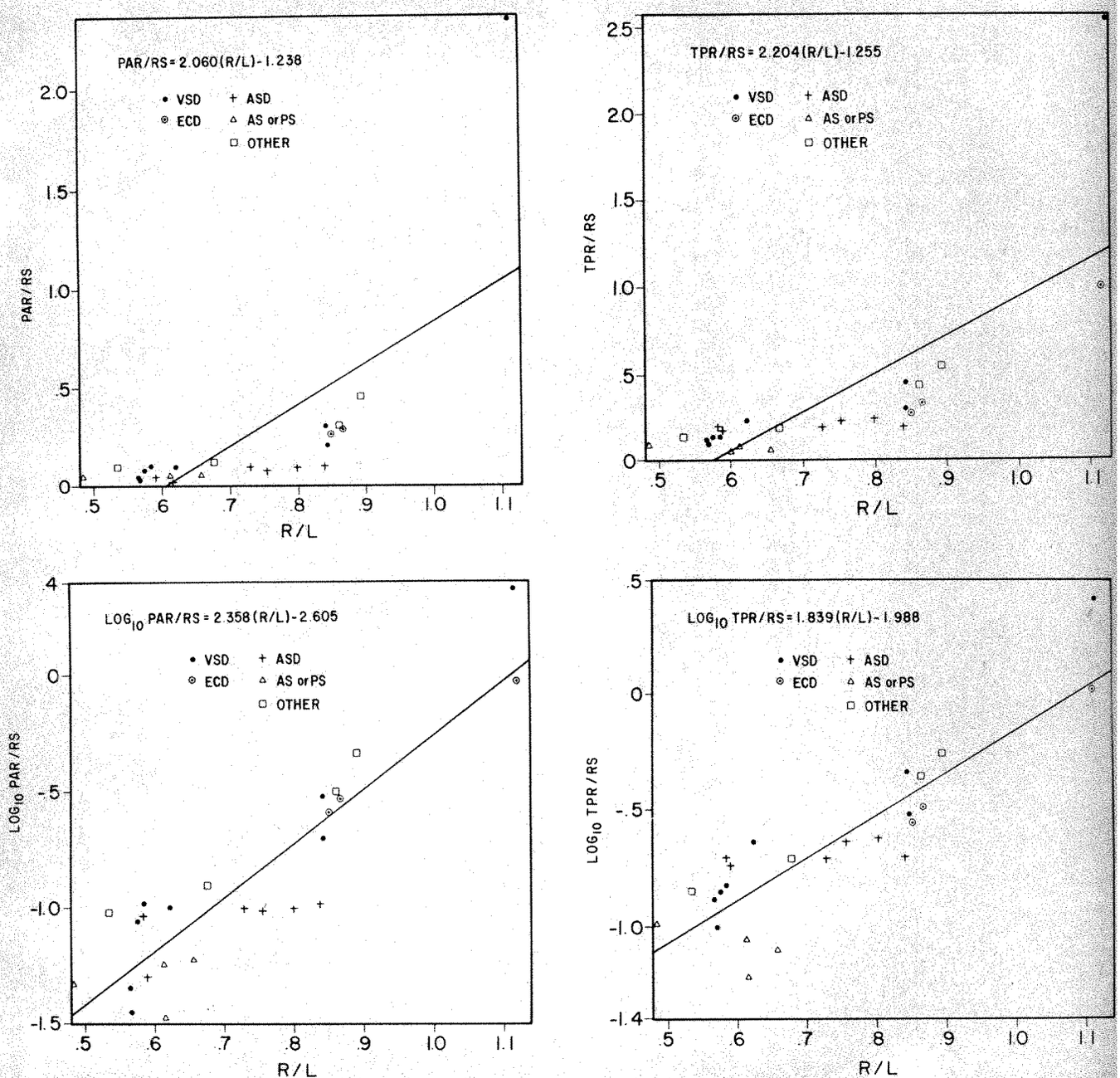


FIGURE 4. R/L (ratio between right ventricular preejection period/right ventricular ejection time and left ventricular ejection period/left ventricular ejection time [RPEP/RVET]/[LPEP/LVET]) plotted against four variables. **Upper left,** R/L versus PAR/RS (pulmonary arteriolar/systemic resistance). The linear regression equation for this relation is PAR/RS = 2.060 (R/L) − 1.238, r = 0.743. There appears to be a significant curvilinear relation between the variables. **Upper right,** R/L is plotted against total pulmonary/systemic resistance (TPR/RS), with a resultant linear regression equation of TPR/RS = 2.204 (R/L) − 1.245, r = 0.749. There also appears to be a significant curvilinear relation between these variables. **Lower left,** R/L is plotted against $\log_{10}$ PAR/RS (pulmonary arteriolar/systemic resistance) with resultant improvement in the correlation coefficient to 0.902. The relation between the variables now appears more linear, and the linear regression equation is $\log_{10}$ PAR/RS = 2.358 (R/L) − 2.605. **Lower right,** R/L is plotted against $\log_{10}$ TPR/RS (total pulmonary/systemic resistance) with a result that is also more linear. The regression equation is $\log_{10}$ TPR/RS = 1.839 (R/L) − 1.988, r = 0.889.

resistance comparing favorably with that obtained by Hirschfeld et al.[3] (r = 0.69 for RPET/RVET versus pulmonary vascular resistance for their data). Also, there was significant deviation from a straight line in the points with higher pulmonary arteriolar resistance and total pulmonary resistance, with the curve resembling a logarithmic function, as did the data points of Hirschfeld et al.[3] The regression equation is pulmonary arteriolar resistance = 44.21 (RPEP/RVET) − 6.20. There was no significant correlation (r = 0.042, r^2 = 0.0017) between the ratio of left ventricular preejection period/left ventricular ejection time (LPEP/LVET) and systemic arteriolar resistance. When right ventricular systolic time intervals were compared with left ventricular systolic time intervals by the ratio of (RPEP/RVET)/(LPEP/LVET) = (R/L) and this ratio was compared with indexes of pulmonary/systemic resistance ratio by linear regression analysis, the correlation coefficients were also significant. Figure 4 (upper left) is the plot of right/left systolic time intervals (R/L) versus pulmonary/systemic resistance ratio (PAR/RS) with resultant correlation coefficient of 0.743 (r^2 = 0.552). At upper right is a plot of right/left systolic time interval ratio (R/L) versus total pulmonary/systemic resistance ratio (TPR/RS) with a correlation coefficient of 0.749 (r^2 = 0.561). Still it can be seen that there is a curvilinear shape to the data curve, resembling a logarithmic function.

For this reason, when R/L is compared with $\log_{10}$ PAR/RS (Fig. 4, lower left), a marked improvement in correlation coefficient to 0.902 (r^2 = 0.814) is noted, because the mathematical model takes into account the deviation of the data points from a straight line. The regression equation for this relation is:

$$\log_{10} \text{PAR/RS} = 2.358\ (\text{R/L}) - 2.605$$

$$\text{PAR/RS} = \text{antilog}_{10}\ [2.358\ (\text{R/L}) - 2.605]$$

and is significant at the P <0.0001 level. The antilog may then be found in a table of logarithms. When R/L is compared with $\log_{10}$ TPR/RS (Fig. 4 lower right), the correlation coefficient is 0.889 (r^2 = 0.790). The regression equation is:

$$\log_{10} \text{TRP/RS} = 1.839\ (\text{R.L}) - 1.988$$

$$\text{TPR/RS} = \text{antilog}_{10}\ [1.839\ (\text{R/L}) - 1.988]$$

and is also significant at the P <0.0001 level. As can be seen from the scatter plot, the data points now conform much more closely to a straight line.

Effect of excluding patients with aortic or pulmonary stenosis: Because severe aortic stenosis changes LPEP/LVET, and severe pulmonary stenosis changes RPEP/RVET, both by prolonging ejection time, it might be expected that excluding patients with a pulmonary or aortic valve gradient greater than 30 mm Hg might further improve the correlation coefficient because it would result in a more homogeneous group. When patients with aortic or pulmonary stenosis (gradient greater than 30 mm Hg) are excluded, regression analysis provides an improvement in correlation coefficient to 0.939 (r^2 = 0.882) with the equation

$$\log_{10} \text{PAR/RS} = 2.468\ (\text{R/L}) - 2.639.$$

When $\log_{10}$ TPR/RS is compared, a correlation coefficient of 0.909 (r^2 = 0.826) results from the equation

$$\log_{10} \text{TRS/RS} = 1.958\ (\text{R/L}) - 2.071.$$

Nonetheless, even with inclusion of the patients with aortic stenosis and pulmonary stenosis, all patients with an R/L of less than 0.84 had a PAR/RS of less than 0.20, which would be considered normal.

Group of patients with ventricular septal defect or complete endocardial cushion defect: The highest correlation coefficient of 0.960 (r^2 = 0.923), as expected, results from the most homogeneous group, consisting of those 11 patients with a ventricular septal defect or a complete endocardial cushion defect, all of whom had a high pressure left to right shunt. Coincidentally, this may be the group pediatric cardiologists would be most interested in, in relation to the development of increasing pulmonary vascular resistance. For this group, the regression equation is:

$$\log_{10} \text{PAR/RS} = 2.465\ (\text{R/L}) - 2.630.$$

Similarly,

$$\log_{10} \text{TPR/RS} = 1.880\ (\text{R/L}) - 1.979$$

for which the correlation coefficient is 0.945 (r^2 = 0.894). From the patient data it is apparent that all patients with a ventricular septal defect or a complete endocardial cushion defect having an R/L of less than 0.85 had a PAR/RS of less than 0.30, which some consider the upper limit for safe operability.

Example: For Patient 21, with an R/L of 0.842, using the previous equation:

$$\log_{10} \text{PAR/RS} = 2.465\ (0.842) - 2.630 = -0.525$$

$$\frac{1}{\log_{10} \text{PAR/RS}} = +0.525$$

$$\frac{1}{\text{PAR/RS}} = 3.350\ (\text{antilog found in table})$$

$$\text{PAR/RS} = 1/3.35 = 0.299,$$

where, in fact, the measured PAR/RS = 0.301.

Discussion

A systolic time interval is a phase of electromechanical systole whose duration is governed by four basic factors: (1) preload, indicated by end-diastolic pressure; (2) afterload, reflected by vascular resistance or arterial diastolic pressure; (3) contractile state of the myocardium; and (4) the rate and sequence of intraventricular electrical conduction.[8,9]

The clinical usefulness of left ventricular systolic time intervals as a bedside method of clinical evaluation has been documented by several investigators.[10–12] Extremely close correlation has been found between conventionally obtained systolic time intervals and those obtained from echocardiograms.[13] The correlation of right ventricular projection period/right ventricular ejection time ratio (RPEP/RVET) with pulmonary ventricular resistance and pulmonary arterial diastolic pressure (afterload) was documented by Hirschfeld et

al.[3] but, as Silverman and Hoffman[4] noted, the correlation was not strong enough to predict pulmonary ventricular resistance accurately, even with their modifications, at least without having determined right ventricular systolic time intervals and pulmonary ventricular resistance at a previous cardiac catheterization. Comparing their methods with those under discussion, several important observations may be made.

Accuracy and limitations of echocardiographic systolic time interval measurements: In determining the preejection period/ejection period ratio, measurements of intervals must be very exact because a small error in timing the opening of a valve will be added to the numerator of a ratio and subtracted from the denominator. Therefore, small errors, by their inclusion in a ratio, become large. For this reason, only complexes with well seen opening and closure movements were included, and they were measured at high paper speed with dial calipers, using scribed parallel rulings made with a drafting triangle. Even so, the choice of the point of onset of the QRS complex and of valve opening and closure is somewhat subjective and therefore prone to error. However, if the same criteria are always used for both the aortic and pulmonary valves, the identical error will be included in both the denominator and numerator of the right/left systolic time interval ratio (R/L), and the two errors will cancel out.

It has been shown that there is significant variation in the onset of the QRS complex in various leads, with the earliest depolarization generally noted in lead V_2.[14] Even if this lead were used (and it was not used in our study or that of Hirschfeld et al.[3]), interpatient variation occurs, and therefore errors are introduced into the determination of the preejection period. Again, with the ratio R/L, the same error is introduced into both the numerator and the denominator, and it is canceled out.

Left ventricular systolic time intervals show little respiratory variation, but right ventricular systolic time intervals show rather large variations with differing phases of respiration.[15] Yet in the study by Hirschfeld et al.,[3] measurements were made only during expiration in older children, and in their infants with high respiratory rates only the shortest systolic time intervals were selected. All phases of respiration were included in our study, because we believed that error would result from exclusion of respiratory variation.

Importantly, in any estimation of pulmonary vascular resistance, very large errors may be made if actual oxygen consumption is not measured for use in the Fick principle flow determinations. Instead, if one uses oxygen consumption values obtained from tables, as Hirschfeld et al. and our laboratory do, an error of up to 40 percent may be made. However, the determination of pulmonary to systemic resistance ratio requires no assumed oxygen consumption values, yet normal limits are well known and frequently used by clinicians.

Effect of left or right ventricular ejection fraction on systolic time interval ratios: In our data and those of previous investigators,[12] there was insignificant correlation between LPEP/LVET and systemic vascular resistance, but others[11] have shown a very strong correlation between this ratio and left ventricular ejection fraction. The effect of a decreasing right ventricular ejection fraction on right ventricular systolic time intervals is not known, but one would presume it also to be significant. As an index of left ventricular ejection fraction, the use of LPEP/LVET in the denominator of the ratio R/L would presumably correct for the effect of decreasing right ventricular ejection fraction on right ventricular systolic time intervals. In contrast to adults, most infants and children with congestive heart failure have failure of both ventricles, although in those with left to right shunt, there is usually high output failure and little diminution of ejection fraction.

For these reasons, while the plot of RPEP/RVET versus pulmonary arteriolar resistance shows increasing variance of the data points with increasing resistance, the plot of R/L versus PAR/RS and TPR/RS (pulmonary arteriolar resistance/systemic resistance and total pulmonary resistance/systemic resistance) shows little increase in variance with increasing PAR/RS or TPR/RS, as multiple sources of introduced error are eliminated or canceled out.

Significance of results in patients with ventricular septal defect and complete endocardial cushion defect: Our data have shown a highly significant correlation for $\log_{10}$ PAR/RS versus R/L and $\log_{10}$ TPR/RS versus R/L. Because stenosis of aortic or pulmonary valves has been shown to prolong ejection time,[12] the effect of excluding patients with a greater than 30 mm Hg peak systolic pulmonary or aortic gradient was investigated. This changed the slope and intercept of the regression line very little but increased the correlation coefficient significantly. Restricting the group to only those with a ventricular septal defect or a complete endocardial cushion defect resulted in the highest correlation coefficient of 0.96, which should have significant predictive value in following up these patients, who are at high risk for the development of pulmonary vascular obstructive disease. The patient data also indicate that all patients with a ventricular septal defect or an endocardial cushion defect having an R/L less than 0.85, have PAR/RS less than 0.30. An R/L greater than 1.0 would suggest a greatly increased PAR/RS. A much larger patient population would improve the confidence limits and will be reported on when patient data have been acquired and analyzed.

Patients with *d*-transposition of the great arteries were specifically excluded from our study at the outset because right and left ventricular activation times are not the same; therefore in these patients the RPEP/RVET ratio cannot be used interchangeably with the LPEP/LVET ratio in normal subjects. Also in *d*-transposition of the great arteries before the Mustard procedure, estimation of pulmonary blood flow is often highly inaccurate because of contributions by bronchial collateral vessels and inaccuracies of most oximeters in the 95 to 100 percent saturation range. Investigation of the systolic time intervals of such pa-

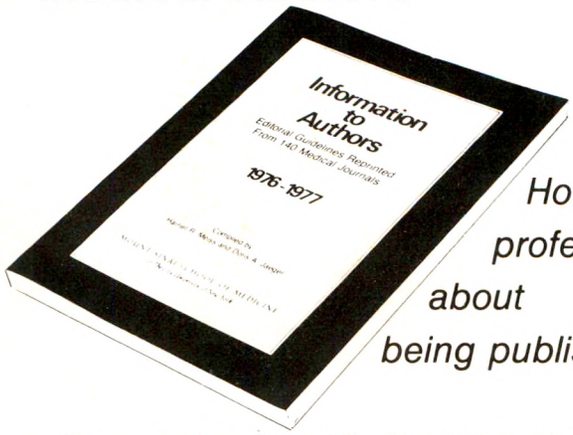
tients is currently being undertaken and will be reported separately.

Clinical implications: Previously, serial cardiac catheterization was the only method for serial evaluation of the pulmonary vascular bed in patients at risk for development of pulmonary vascular obstructive disease. Although determination of echocardiographic right systolic time interval ratios at the time of catheterization may allow subsequent estimation of pulmonary ventricular resistance and pulmonary arterial diastolic pressure at later dates, no method previously described allowed accurate estimation of pulmonary ventricular resistance or pulmonary arteriolar resistance/systemic arteriolar resistance ratio before catheterization. The use of the regression equations described should allow at least a rough estimation of pulmonary arteriolar resistance/systemic arteriolar resistance, and more accuracy can be expected if patients with aortic stenosis or pulmonary stenosis can be excluded, or if the patient has a ventricular septal defect or a complete endocardial cushion defect. This should prove useful to clinicians in the timing, or avoidance altogether, of cardiac catheterization with its attendant risk and expense.

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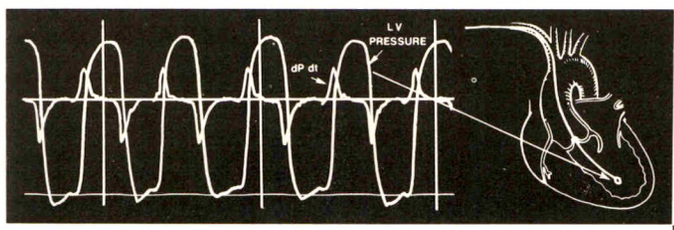
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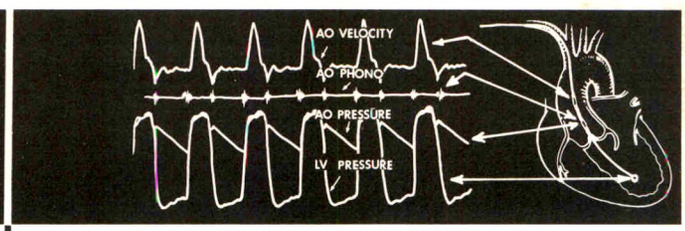
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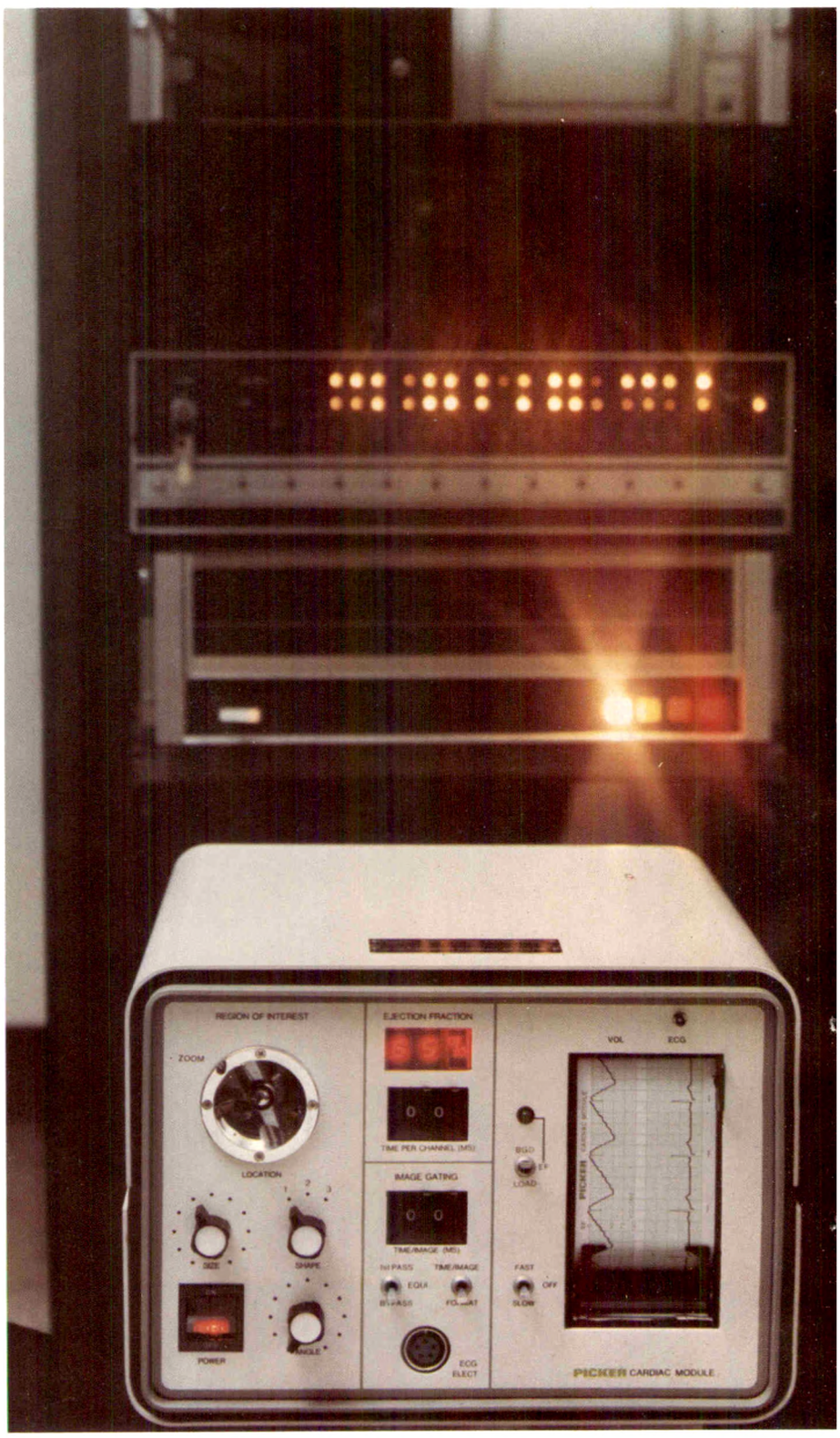
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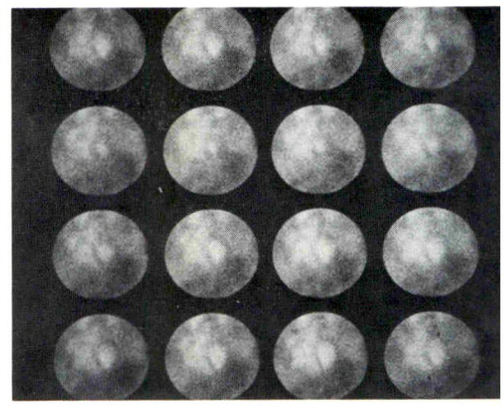


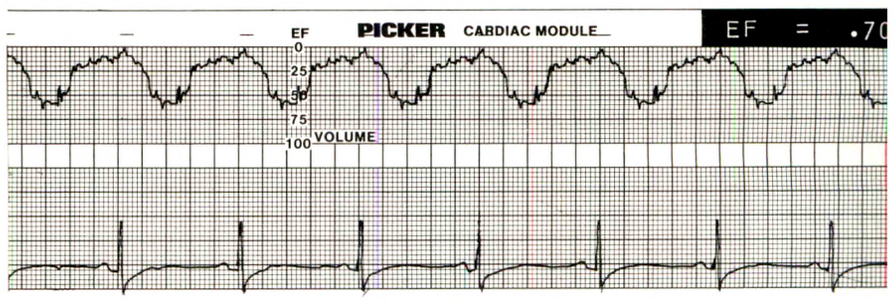
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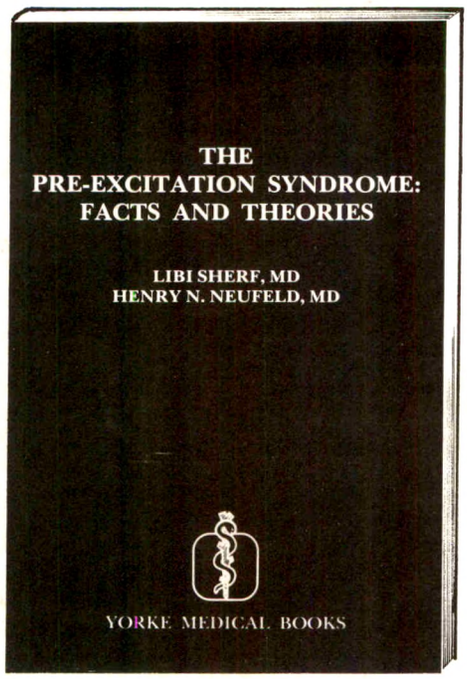






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The 13 Chapters Are a Comprehensive Summary

1. General Considerations
2. The Electrocardiogram in the Pre-excitation Syndrome: Complexes and Configurations
3. The Electrocardiogram in the Pre-excitation Syndrome: Disturbances of Rate and Rhythm
4. Pathology
5. Noninvasive Methods of Investigation
6. Invasive Methods of Investigation
7. Prognosis
8. Treatment
9. Problems of Diagnosis — Some Illustrative Cases
10. Summary of Findings and Theories of Pre-excitation Syndrome
11. Concept of Interacting Structural and Functional Factors
12. Explanation of Some Phenomena of the Pre-excitation Syndrome by the Proposed Concept
13. Various QRS Patterns in the Different Forms of Pre-excitation

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals

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HOLD IT

THE NEW MIREL™ PACEMAKER FROM MEDTRONIC®

YOU HAVE TO HOLD IT TO APPRECIATE IT.

We've managed to compress the new Medtronic lithium pacemaker into a smaller, thinner, yet contoured shape. But a photo doesn't do it justice. We want you to actually feel and touch a Mirel pacemaker. So Medtronic will send you a Mirel demo unit* with no obligation. Just write—on your professional letterhead—to Mirel Demo, Medtronic, Inc., Station 369, P.O. Box 1453, Minneapolis, MN 55440 USA. Physicians only. Limit one demo per physician. This offer is made only to physicians residing in the United States of America and Canada.



Medtronic

SEE FOLLOWING PAGE FOR MORE DETAILS ON THE MIREL PACEMAKER FROM MEDTRONIC.

*This demonstration unit does not contain battery or electronics, but approximates the Mirel pacemaker's physical characteristics—such as connector, size, shape and weight. Packaged in a handsome jewelry case, it is ideal for showing to patients, demonstrating at seminars, etc.

SHOWN ACTUAL SIZE

THE NEW MIREL™ PACEMAKER FROM MEDTRONIC®

Our new lithium-powered Mirel pacemaker is so compact—yet it contains all the performance features you've come to expect from Medtronic lithium pacemakers, including Constant Rate, Constant Energy, superior electromagnetic interference protection and more. And although the Mirel pacemaker is a step down in size, it's a step up in quality. This unique combination of smaller size plus a design that provides improved reliability and quality is possible due to Medtronic's exclusive advances in microcircuitry.

Simplified Assembly for High Reliability.

The Mirel pacemaker has only 21 separate components as compared to 40 in its lithium predecessor. Benefit: less chance of component failure, fewer connections subject to failure. Mirel pacemaker components are fused by resistance welding rather than soldering. Benefit: reduced possibility of contamination.

The Mirel pacemaker uses hermetically sealed mini-paks inside hermetically sealed hybrids. Benefit: circuitry is enclosed in a redundant protected environment—an additional safety feature for your patients. And, these "mini-paks" are easily and repeatedly tested before they are connected to the hybrid substrate. Tests include centrifuge, temperature and burn-in cycles, hermeticity, shock and, of course, visual microscopic inspection.

Pacing for Life™ Warranty

Another advantage, all Mirel-VL (ventricular-long-lived) pacemakers are covered by the Medtronic *Pacing for Life*™ warranty. If, during the life of your patient, the Mirel-VL pacemaker fails for any reason, Medtronic will provide a replacement product at no charge and give the same warranty on the replacement product.

There's much more to the Mirel story. Ask your Medtronic representative for details.

MEDTRONIC® IMPLANTABLE PULSE GENERATORS

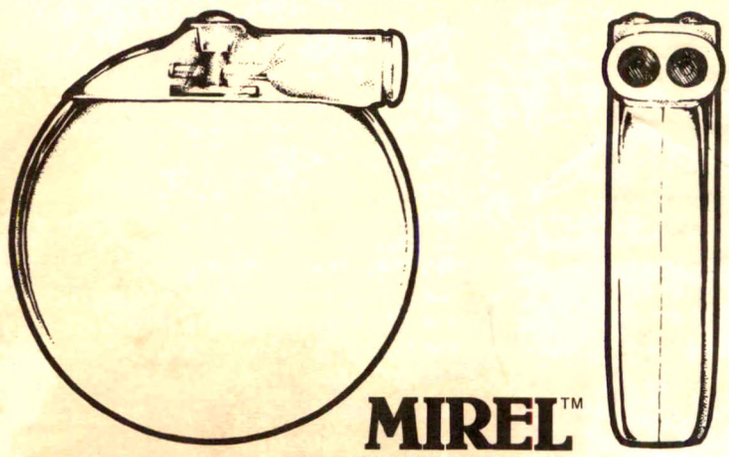
Intended Uses—Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).

Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

Precautions—The physician should be aware that all pulse generators will ultimately cease to function and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

Side Effects—Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.



MIREL™

SHOWN ACTUAL SIZE

(Typical Physical Specifications)

Weight—60 grams • Diameter—53 mm

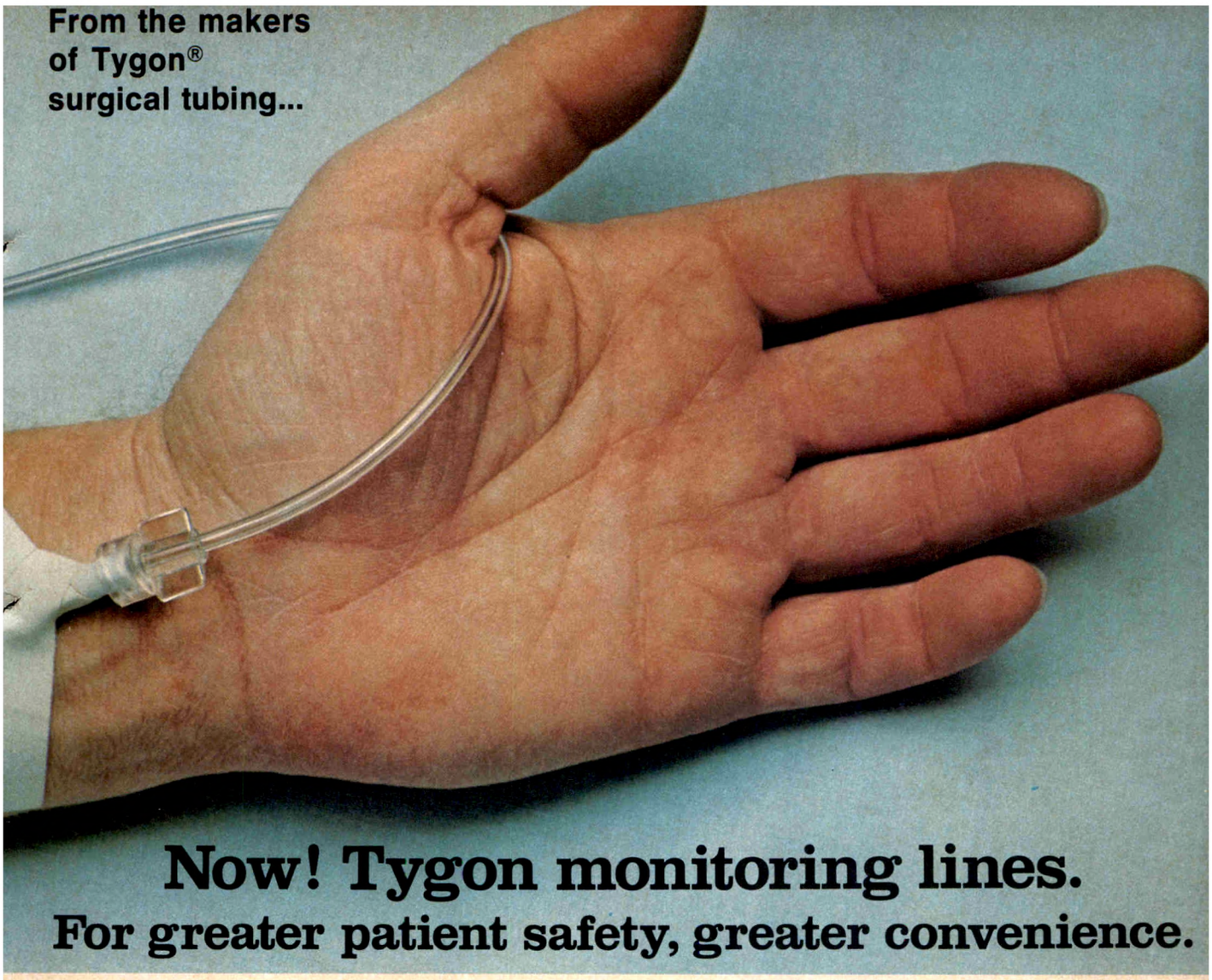
Thickness (center)—15 mm • Thickness (edge)—11 mm

Available in unipolar and bipolar configuration.

Mirel™-VL has 2.2 amp hour lithium-iodine power source.

Mirel™-VM has 1.8 amp hour lithium-iodine power source.

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Now! Tygon monitoring lines.

For greater patient safety, greater convenience.

The new Tygon family of monitoring/administration lines brings to the medical profession significant safeguards and conveniences found in no other monitoring lines.

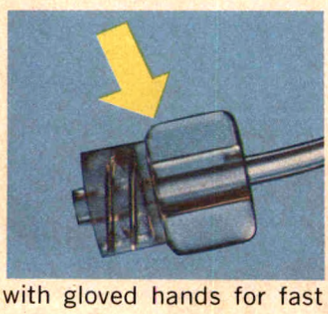
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From end to end, Tygon monitoring/administration lines are clear. Not only the tubing, but the fittings as well. This offers an important advantage: easier, positive visual checking for air bubbles or other emboli — at a glance.

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The sturdy Tygon tubing walls assure faithful transmission of pressure without loss, unlike soft-walled tubing.

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Each Tygon monitoring/administration line is sterile-packaged in a peel-open pouch and is designed for single patient use.

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Tygon® tubing, a product of the Norton Company, has earned a reputation for undeviating excellence in the health care field...particularly where critical procedures are concerned.

Tygon monitoring/administration lines are formulated and produced with this same uncompromising attention to excellence. From raw material to finished product, Norton alone has total manufacturing responsibility. This way, Norton can completely control and maintain the high quality that the medical profession expects from the trusted name "Tygon".

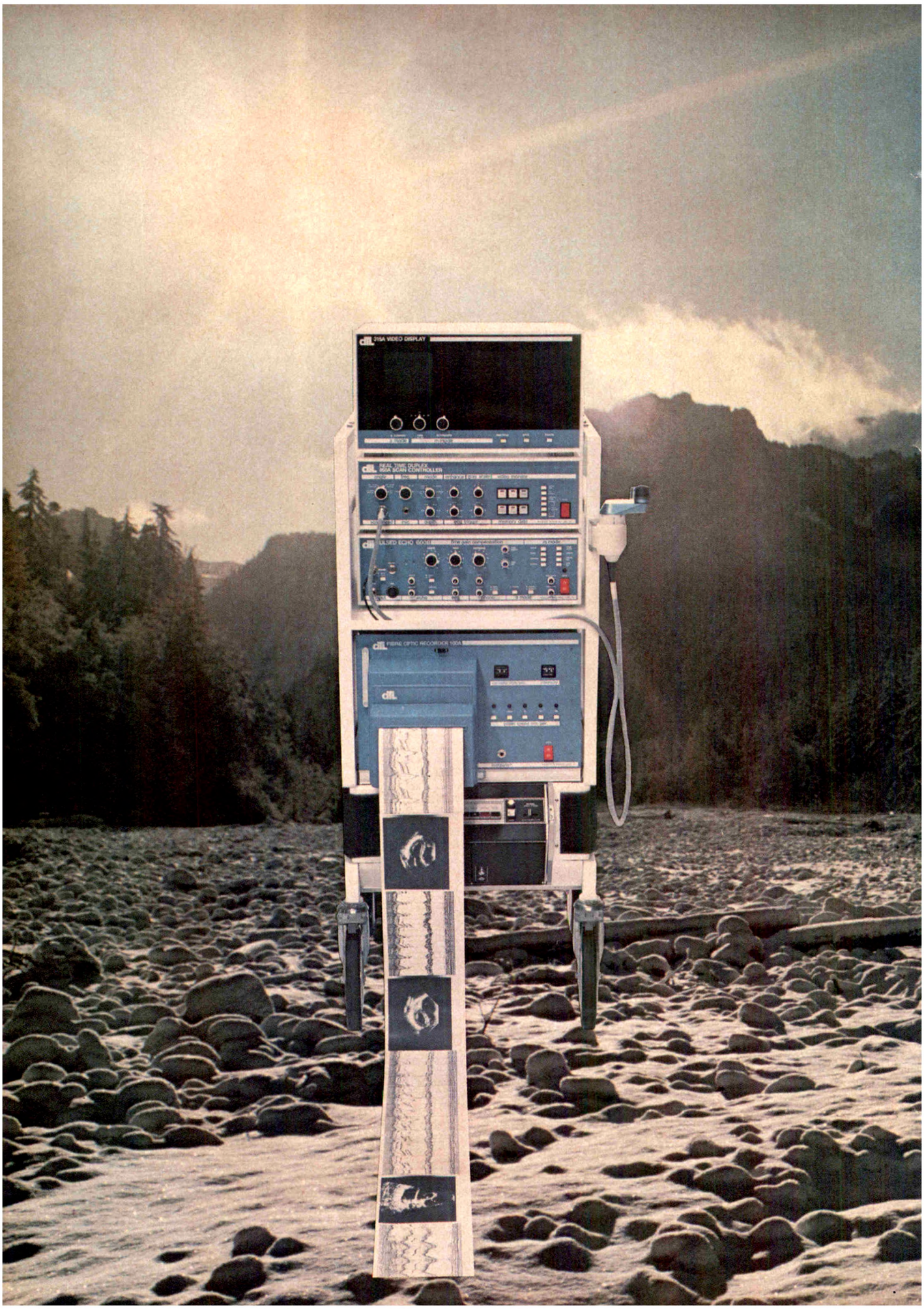


For detailed information on Tygon monitoring/administration lines including sizes, end connector options, and selection data, write for Bulletin MA-1000. Better yet, call Norton toll-free 800-321-9634 (Ohio call collect 216-630-9230).

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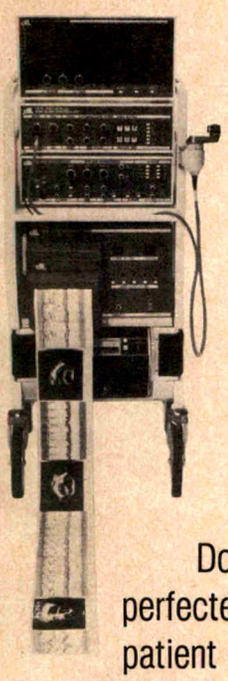
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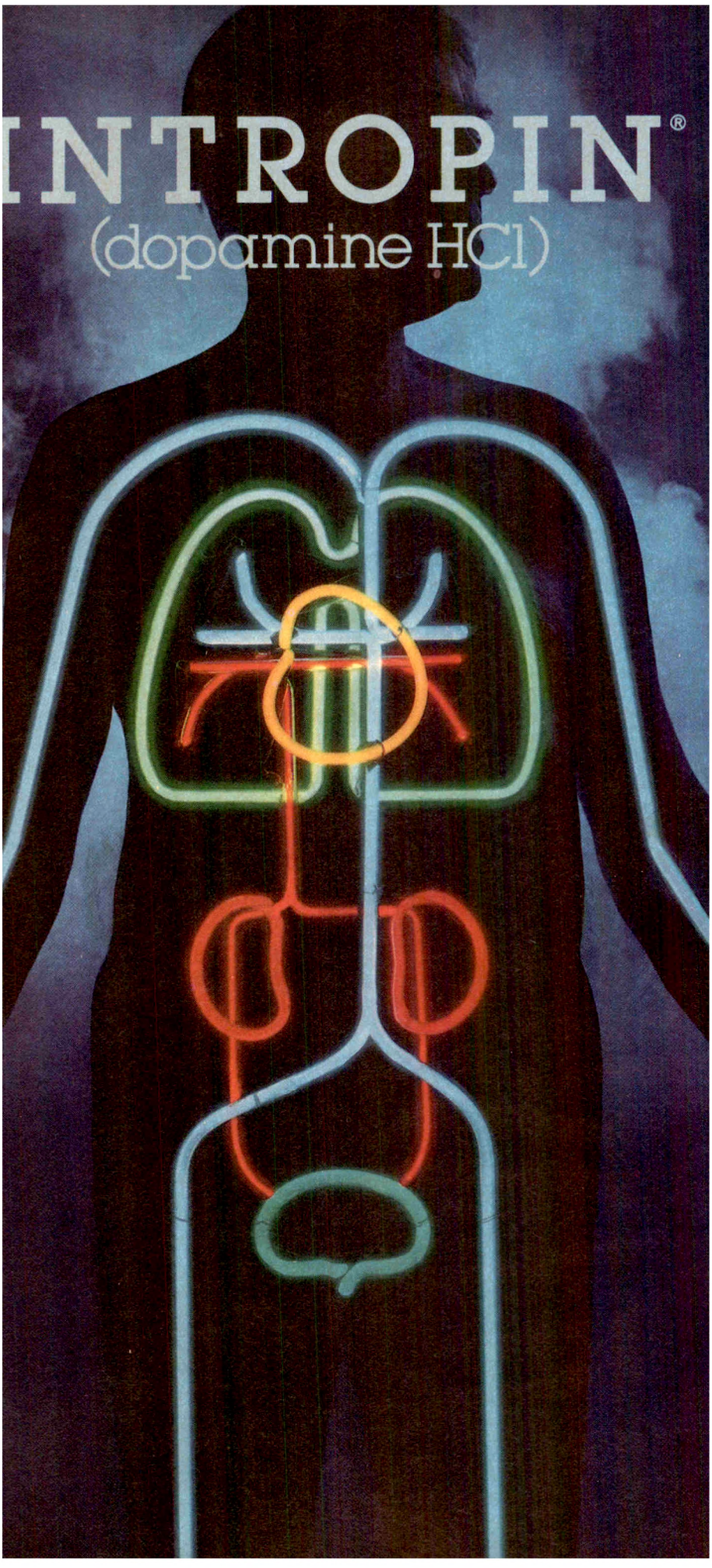
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INTROPIN®
(dopamine HCl)

In the shock syndrome:

Selectively redirects blood to vital organs

Increases vital organ perfusion

In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

Maintains kidney function

The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

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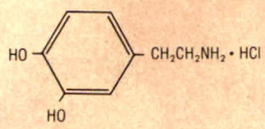
INTROPIN® (dopamine HCl)

(See last page of this advertisement for full prescribing information.)

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output – Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy – Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required – Close monitoring of the following indices – urine flow, cardiac output and blood pressure – during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution – Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration – INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized..

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

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"An excellent addition to the library of every dermatologist . . . research worker . . . resident in dermatology." *Archives of Dermatology*

Psoriasis: Proceedings of the Second International Symposium, edited by Eugene M. Farber, MD, and Alvin J. Cox, MD, 487 pp. 225 + illus, $35, New York, Yorke Medical Books, 1977.

The proceedings of the Second International Symposium on Psoriasis, which was held at Stanford University from July 12 through 15, 1976, have been published in a handsome volume that is a great improvement over that of the 1971 symposium. The type is clear and can be read easily, and the many graphs and photographs consistently are reproduced well. There are few errors, and the editors are to be congratulated.

The opening remarks of the symposium by Dr G. Donald Whedon, director of the National Institute of Arthritis, Metabolism, and Digestive Diseases, are of particular interest. In essence, Dr Whedon acknowledged the effects of lobbying by institutions and individuals to obtain money for research on psoriasis. Of particular note was the urging of the National Institute for Arthritis, Metabolism, and Digestive Diseases by the Senate Appropriations Subcommittee for Health, Education, and Welfare to increase its efforts in funding research on psoriasis; the Institute was directed also to analyze the needs and priorities for dermatologic research. It is this kind of direct plotting that will be needed to obtain more funds for dermatologic research.

The papers are presented uniformly. Some of the chapters are especially outstanding, such as the chapter by Van Scott and Yu, "Pharmacobiologic Leads in Psoriasis," and the chapter by Stoughton, "A Perspective of Topical Corticosteroid Therapy." The bibliographic references were carefully selected and up-to-date and will add to the reference value of this volume.

My only criticism of the book is the absence of an index—an addition that would make the book more useful.

This book will bring the reader reasonably up-to-date with the old and the new ideas in the treatment and research in psoriasis. It would be an excellent addition to the library of every dermatologist, as well as research workers in the field, and certainly should be available to all residents in dermatology.

SIGFRID A. MULLER, MD
Rochester, Minn

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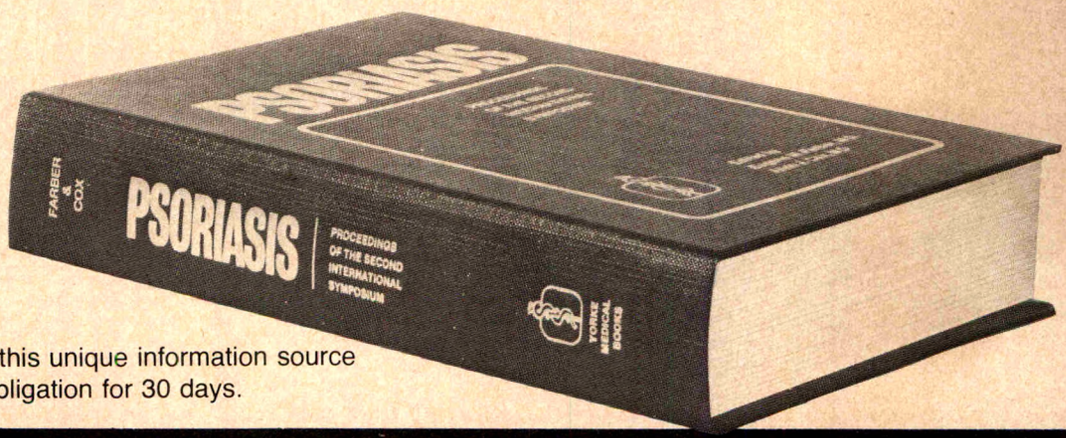
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Edited by EUGENE M. FARBER, M.D.,
Chairman, Department of Dermatology, Stanford University
and ALVIN J. COX, M.D.
Professor of Pathology in Dermatology, Stanford University
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Isoproterenol as a Potential Pulmonary Vasodilator in Primary Pulmonary Hypertension

FUHEID S. DAOUD, MD
JOHN T. REEVES, MD*
DENNIS B. KELLY, MD

Lexington, Kentucky

The effects of various pharmacologic agents on pulmonary arterial pressure and vascular resistance were studied in six patients considered to have primary pulmonary hypertension at the time of cardiac catheterization. Vascular resistance increased slightly after the administration of hypoxic air in two patients; it decreased after the administration of 100 percent oxygen in one patient. After the intravenous administration of diphenhydramine and sodium salicylate, drugs that block the actions of the powerful pulmonary vasoconstrictors histamine and prostaglandin ($F\alpha_2$), vascular resistance did not change in two patients. After the intravenous administration of hydrocortisone, vascular resistance decreased significantly in one patient but only slightly in four others. Vascular resistance did not change significantly after the administration of the immunosuppressive agents prednisone and azathioprine in three patients. These results suggest that neither hypoxia, histamine nor prostaglandin plays a role in the etiology of primary pulmonary hypertension. The possible role of an immune mechanism needs further investigation.

Vascular resistance decreased after the acute intravenous administration of the potent pulmonary vasodilator isoproterenol (0.5 to 2 μg/min) in five of the six patients. Both pulmonary pressure and resistance decreased in two patients and there was no change in pressure in one patient after the "subacute" administration of isoproterenol (0.5 to 1 μg/min) for 5 to 12 days. In all patients both values returned to control level when isoproterenol was discontinued. The sublingual administration of isoproterenol (15 mg) significantly decreased vascular resistance in one patient but not in the other three patients studied. The one patient who responded has been receiving maintenance doses of isoproterenol for 30 months. We conclude that isoproterenol is not uniformly effective in all patients, but that it is a useful therapeutic agent in patients who respond.

The pathogenesis of primary pulmonary hypertension is unknown. Morphometric[1] and microradiographic[2] studies of the lungs of patients who die with this disease suggest a vasoconstrictive origin. This hypothesis is further supported by the observation that in some patients, the administration of pulmonary vasodilators such as tolazoline hydrochloride,[3–5] acetylcholine[6,7] and isoproterenol[8,9] decreases pulmonary arterial pressure and vascular resistance. However, attempts to ameliorate the course of this progressive and fatal disease with these drugs have been unsuccessful. Recently, Rao et al.[8] studied the effects of acute and chronic intrapulmonary administration of isoproterenol in a 12 year old boy and reported that pulmonary arterial pressure decreased after the acute administration of isoproterenol. However, the patient died from complications, and the long-term effect of the drug could not be determined.

This report describes the systematic study of the responses to various pharmacologic agents in six patients considered to have primary pul-

From the Cardiovascular Division, Department of Medicine, University of Kentucky, Albert B. Chandler Medical Center, Lexington, Kentucky. Manuscript received April 19, 1976; revised manuscript received May 30, 1978, accepted May 31, 1978.

*Present address: Department of Medicine, University of Colorado, Denver, Colorado.

Address for reprints: Fuheid S. Daoud, MD, Department of Cardiology, Bethesda Hospital, 619 Oak Street, Cincinnati, Ohio 45206.

TABLE I

Initial and Repeat Hemodynamic Studies in Six Patients Considered to Have Primary Pulmonary Hypertension

Case	Age at Time of Study (yr)	Months From Onset of Symptoms	Other Significant Diseases	Mean Pressure RA	Mean Pressure Ppa	Mean Pressure Ao	Q_{pulm}	CI	PVR	PaO_2	$PaCO_2$	pH
1	27	10	. . .	4	53	83	3.1	1.9	15	80	31	7.40
		22		4	47	75	4.4	2.7	9	56	27	7.48
2	28	11	. . .	4	56	90	3.6	2.5	14	74	44	7.47
		23		8	84	92	1.4	1.0	56	64	35	7.45
3	39	2	LE	8	90	127	2.5	1.5	34	76	37	7.39
		50		20	88	88	3.1	1.8	23	66	31	7.42
4	31	29	. . .	4	40	88	3.6	2.1	9	87	30	7.46
5	22	5	. . .	10	71	82	2.2	1.5	30	61	25	7.45
6	17	12	. . .	5	70	75	3.4	2.1	18	92	19	7.46

AO = aortic pressure (mm Hg); CI = cardiac index (liters/min per m^2); LE = lupus erythematosus; $PaCO_2$ = arterial carbon dioxide tension (mm Hg); PaO_2 = arterial oxygen tension (mm Hg); pH = arterial pH; Ppa = pulmonary arterial pressure (mm Hg); PVR = pulmonary vascular resistance units); Q_{pulm} = cardiac output (liters/min); RA = right atrial pressure (mm Hg).

monary hypertension. In evaluating these patients we considered several postulated mechanisms of the increase in pulmonary pressure and resistance characterizing this disorder. These included locally produced vasoconstricting substances such as histamine[10,11] and prostaglandins[12,13] as well as the possibility that the disease may be autoimmune in nature.[14–16] In light of these postulated mechanisms, we studied the effects of pharmacologic blocking agents including diphenhydramine (Benadryl®), sodium salicylate and cortisone[17] and the immunosuppressive drugs prednisone and azathioprine (Imuran®) on pulmonary arterial pressure and vascular resistance. In addition, we sought to establish the usefulness of these drugs and others, including isoproterenol and 100 percent oxygen, in the management and course of patients with primary pulmonary hypertension.

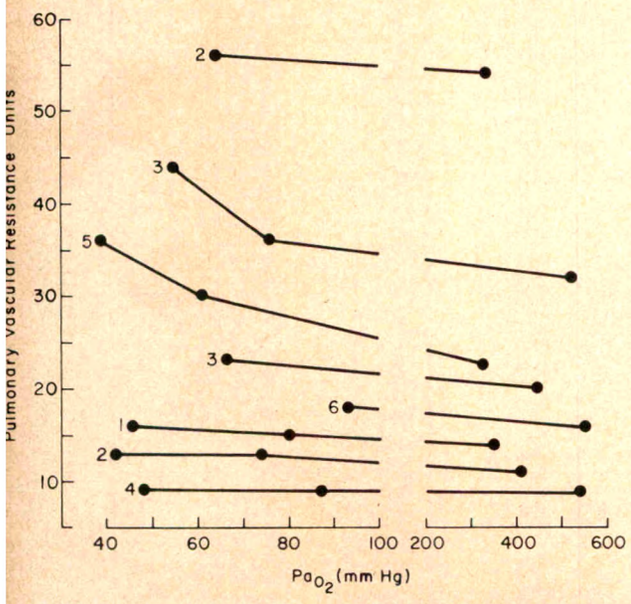


FIGURE 1. Effects of hypoxia and hyperoxia in six patients with primary pulmonary hypertension. Case numbers indicated. Patients 2 and 3 were restudied 2 and 4 years, respectively, after the initial study. Pa_{O_2} = arterial oxygen tension.

Material and Methods

Patients: The study was performed in six patients referred to the University of Kentucky Medical Center between 1969 and 1974. The diagnosis of primary pulmonary hypertension was based on the following criteria: pulmonary hypertension in the absence of (1) pulmonary parenchymal disease as determined from X-ray film, blood gas levels and pulmonary function tests; (2) intracardiac shunt or left-sided cardiac disease as assessed with catheterization; and (3) any evidence of pulmonary emboli as evaluated with pulmonary angiography or lung scan, or both.

Cardiac catheterization: Studies were performed after an overnight fast in a nonmedicated state. Right heart catheterization was performed with either a Cournand or a Swan-Ganz balloon-tipped catheter. Left heart pressures were measured using a no. 7 catheter (National Institutes of Health) introduced by way of a brachial arterial cutdown or a no. 7 Gensini catheter advanced percutaneously by way of the femoral artery. In the patients who underwent multiple repeat catheterizations, the percutaneous approach by way of the femoral vessels was utilized. Cardiac output was measured with the indocyanine (Cardio-green®) dye-dilution or thermodilution method.

After control measurements of pressures, cardiac output and arterial blood gases were obtained, various pharmacologic agents were administered in the following sequence: hypoxia, 100 percent oxygen, intravenous isoproterenol, sublingual isoproterenol, cortisone, diphenhydramine (Benadryl) and sodium salicylate. Cardiac output, blood gases and pressures were again measured when pulmonary arterial pressure was stable. After each intervention, pressures and cardiac output were allowed to return to control level before the next drug was administered.

Pulmonary angiography was performed with the patient breathing 100 percent oxygen after the intravenous administration of 10,000 units of heparin. Pulmonary vascular resistance, expressed in units, was calculated as the pressure gradient between mean pulmonary arterial and mean pul-

monary wedge pressures divided by pulmonary blood flow. An acute intervention was considered to cause a change in resistance when the resistance increased or decreased by more than 20 percent of the control value.

Results

Clinical and hemodynamic data (Table I): Five women and one man, aged 17 to 38 years (average 28), were studied. The duration of symptoms at the time of the initial hemodynamic study ranged from 2 to 36 months (mean 21). In three patients (Cases 3, 4 and 6), the onset of symptoms was preceded by an upper respiratory infection. All of the patients had the characteristic clinical features of primary pulmonary hypertension, as well as fatigue, dyspnea on exertion and syncope. Three patients (Cases 2, 3 and 4) had angina-like chest pain, and two (Cases 4 and 6) had pleuritic pain. The two patients with pleuritic pain also reported episodes of hemoptysis and in one of these two patients the hemoptysis was associated with fever and pulmonary infiltrates. Cyanosis and clubbing were present in three patients (Cases 2, 4 and 5).

On admission, all patients had a dominant *a* wave, accentuated pulmonary closure sound and a systolic murmur (left sternal border). The chest roentgenogram on the initial examination demonstrated cardiomegaly in four patients, with prominence of the main pulmonary trunk and its main branches but attenuation of peripheral branches in all six. All patients manifested right ventricular hypertrophy, with or without right atrial enlargement electrocardiographically, and increased right ventricular dimensions on echocardiography. Pulmonary function studies, including spirometry and diffusion studies, performed in five patients, revealed normal findings. Results of lung scans using Technetium-99, performed in four patients, (Cases 1, 2, 4 and 6), were normal. Only two of the six patients are still alive. Postmortem examination was not performed in those who died.

Left ventricular end-diastolic and pulmonary wedge pressures measured at the time of the initial and repeat studies ranged from 4 to 8 mm Hg in the six patients. Initial cardiac output measurements ranged from 2.2 to 3.6 liters/min (mean 3.0). Mean pulmonary arterial pressures ranged from 40 to 90 mm Hg (mean 63). Mean right atrial pressures were above 5 mm Hg in the three patients who had clinical signs of right heart failure at the time of the study. Three patients had arterial oxygen tension measurements of less than 80 mm Hg on the initial study. Hematocrit values ranged between 40 and 51 percent.

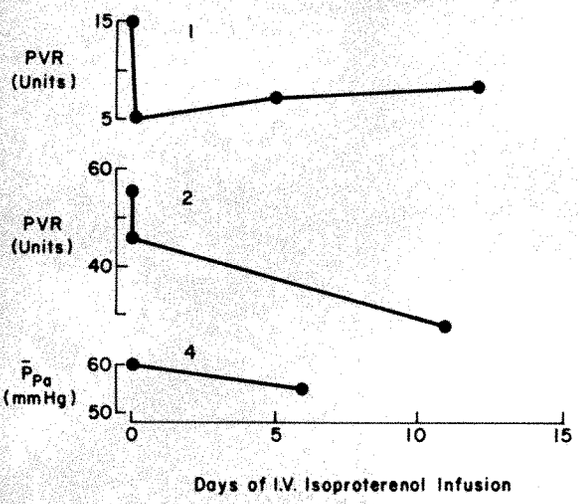
Hypoxia and hyperoxia (Fig. 1): In five patients breathing 10 to 13 percent oxygen for 5 to 8 minutes, the arterial oxygen tension levels decreased to 39 to 55 mm Hg. Pulmonary vascular resistance increased by at least 20 percent from room air control values only in Patients

TABLE II

Hemodynamic Effects of Acute and Chronic Intravenous Administration of Isoproterenol (ISP) in Six Patients Considered to Have Primary Pulmonary Hypertension

Case	Date of Study	State	Mean Pressures Ppa	Ppa-Pc	Ao	Q_{pulm}	CI	PVR	PaO_2
1	2/24/72	Control (0 day of study)	53	47	83	3.1	1.9	15.2	80
		ISP (1 μg/min)	30	24	82	4.8	2.9	5	103
	2/29/72	5 days of ISP (0.5 μg/min)	30	24	84	3.6	2.2	6.7	95
	3/6/72	12 days of ISP (0.5 μg/min)	44	38	84	4.4	2.7	8.6	72
	3/13/74	Control (0 day of study)	47	41	75	4.4	2.7	9.3	56
		ISP (0.5 μg/min)	42	36	76	6.5	3.9	5.5	80
	3/16/74	3 days of ISP (0.5 μg/min)	34	28	72	3.6	2.2	7.8	71
2	4/21/70	Control	56	50	90	3.6	2.5	13.9	74
		ISP (2 μg/min)	60	54	92	5.1	3.5	10.6	75
	4/6/72	Control (0 day of study)	84	78	92	1.4	1.0	56.3	64
		ISP (2 μg/min)	103	97	102	2.1	1.4	46.2	. . .
	4/17/72	11 days of ISP (1 μg/min)	64	59	78	2.1	1.4	28.0	88
3	5/27/69	Control	90	86	127	2.5	1.5	34.4	76
		ISP (2 μg/min)	110	106	118	3.5	2.1	30.3	. . .
	5/15/73	Control	82	74	100	3.1	1.8	23.9	66
		ISP (2 μg/min)	94	86	89	4.0	2.4	19.5	. . .
4	12/13/72	Control	40	36	88	3.6	2.1	10.0	87
		ISP (1 μg/min)	45	39	84	4.4	2.6	8.9	. . .
	6/10/73	Control (0 day of study)	60	. . .	86	. . .	. . .	. . .	59
	6/16/73	6 days of ISP (1 μg/min)	55	. . .	86	. . .	. . .	. . .	39
5	4/4/73	Control	68	63	86	2.2	1.5	28.6	. . .
		ISP (1 μg/min)	80	75	82	3.4	2.3	22.0	. . .
6	5/28/74	Control	64	58	82	3.2	2.13	18.1	93
		ISP (1 μg/min)	85	79	72	5.0	3.3	15.8	. . .

Ao = aortic pressure (mm Hg); CI = cardiac index (liters/min per m^2); PaO_2 = arterial oxygen tension (mm Hg); Pc = pulmonary wedge pressure (mm Hg); Ppa = pulmonary arterial pressure (mm Hg); Q_{pulm} = cardiac output (liters/min); PVR = pulmonary vascular resistance (units).



IGURE 2. Effect on pulmonary vascular resistance (PVR) or on mean ulmonary arterial pressure ($\bar{P}_{Pa}$) of a continuous intravenous (I.V.) nfusion of isoproterenol, 0.5 to 1.0 μg/min, in Patients 1, 2 and 4. 'atients 1 and 2 had a sustained decrease in pulmonary vascular re- istance, but Patient 4 had no relief of pulmonary hypertension.

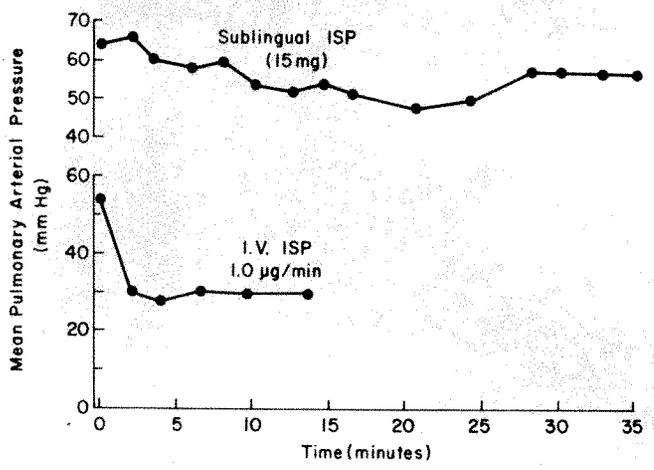


FIGURE 3. Patient 1. Time course of the effects of sublingual and intravenous (I.V.) administration of isoproterenol (ISP) on pulmonary arterial pressure. Note the prompt and larger decrease in pressure with intravenous as compared with sublingual isoproterenol.

and 5. Breathing 100 percent oxygen increased the rterial oxygen tension to 335 to 550 mm Hg, but pulnonary vascular resistance decreased from the room air ontrol value only in Patient 5.

Diphenhydramine and sodium salicylate: The ntravenous administration of 25 mg of diphenhydraine increased the pulmonary arterial pressure from 6 to 58 mm Hg in Patient 1 but caused no significant hange in Patient 2 (88 mm Hg before, 84 mm Hg after). he pulmonary vascular resistance, measured in Patient , also did not change (46 and 52 units). In these two atients, the intravenous administration of 1 g of sodim salicylate did not decrease pulmonary arterial ressure (52 and 60 mm Hg in Patient 1 and 88 and 88 m Hg in Patient 2). The pulmonary vascular resisance was unchanged in Patient 2 (41 and 43 units).

Corticosteroid and azathioprine: The intravenous dministration of 100 mg of hydrocortisone to Patient decreased pulmonary vascular resistance from 13 to units without decreasing mean aortic pressure or ardiac output. Pulmonary arterial pressure and resisance did not return to control values in 30 minutes of bservation. The pulmonary vascular resistance after ydrocortisone was unchanged in Patient 2 (45 units efore, 45 units after), Patient 4 (9 and 7 units), Patient (24 and 23 units) and Patient 6 (17 and 14 units).

The administration of 40 to 60 mg of prednisone daily or 3 to 6 months caused no improvement in the clinical tatus in Patients 1, 2 and 4. The administration of zathioprine, 100 mg daily for 3 and 24 months, repectively, was accompanied by subjective improvement n Patients 1 and 2, but pulmonary arterial pressure was ot reduced. Patient 4 died during the 6th month of zathioprine therapy. The chronic administration of orticosteroids or azathioprine was without objective vidence of benefit to these three patients.

Intravenous isoproterenol, acute and subacute effects (Table II): The intravenous administration of isoproterenol (0.5 to 1.0 μg/min) acutely decreased pulmonary vascular resistance by more than 20 percent in Patients 1, 2 and 5. Cardiac output increased in all patients, and the arterial oxygen tension, when measured, did not decrease.

Three patients consented to remain in the hospital for continued intravenous isoproterenol therapy. Patients 1, 2 and 4 received continuous intravenous administration of isoproterenol (0.5 to 1.0 μg/min) for 5 to 12 days (Fig. 2). In Patients 1 and 2 the pulmonary vascular resistance decreased. In Patient 4 the pulmonary arterial pressure did not decrease, but the arterial oxygen tension decreased to 39 mm Hg and then returned to the preisoproterenol control value 3 days after the infusion was discontinued.

Sublingual isoproterenol (Fig. 3): In Patient 1, sublingual isoproterenol, 15 mg, decreased the mean pulmonary arterial pressure from 66 to 46 mm Hg and pulmonary vascular resistance from 14 to 9 units. The minimal pressure occurred at 20 minutes, and by 35 minutes pressure had not quite returned to control values. The decrease in pulmonary arterial pressure was not as large or as prompt as with the intravenous administration. Sublingual isoproterenol did not change pulmonary vascular resistance in Patient 2 (28 units before, 26 units after), Patient 5 (24 and 23 units) or Patient 6 (17 and 16 units).

Because of her good response, Patient 1 has been receiving maintenance doses of sublingual isoproterenol for 30 months. Because of symptoms requiring increasing doses, she has been hospitalized five times for 3 to 4 days of continuous intravenous isoproterenol therapy. After each hospitalization, her requirements for sublingual isoproterenol are reduced. She is now taking sublingual isoproterenol (up to 20 tablets daily), which she believes is particularly useful before exertion.

Her most recent cardiac catheterization (March 1974, Table I) indicated no deterioration in pulmonary hemodynamic status.

Discussion

Possible pathophysiologic mechanism of primary pulmonary hypertension: Pulmonary vasodilators such as tolazoline, acetylcholine, isoproterenol and oxygen have been reported to decrease acutely pulmonary arterial pressure and resistance in some patients with primary pulmonary hypertension.[3–9] In these patients some degree of vasoconstriction was presumed to have been present. In this study we considered three possible mechanisms of vasoconstriction:

I. *The disease process could represent an augmentation of the pulmonary pressor response to hypoxia, a known potent pulmonary vasoconstrictor.* If such were the case one might expect a large decrease in pulmonary vascular resistance with oxygen breathing and, in particular, a large increase with alveolar hypoxia. However, 100 percent oxygen failed to cause a significant reduction in resistance in seven of eight patients described by Shephard et al.[18] and in the one patient described by Marshall et al.[6] In all four of our six patients neither hyperoxia nor hypoxia caused large changes in pulmonary vascular resistance. It seems unlikely that augmentation of the hypoxic pulmonary pressor response was an etiologic factor in the disease process of these patients. Further, because of the small response to 100 percent oxygen in the present and previous reports, and the high level of alveolar oxygen tension (even though the arterial level of partial pressure of oxygen [PO_2] may be low) reported for such patients, hypoxic vasoconstriction probably is not a major factor in the pathogenesis of the disease.

II. *Vasoconstrictor agents may accumulate near the small pulmonary arteries and initiate or potentiate pulmonary hypertension.* Alpha adrenergic stimulation after catecholamine release was early considered a possibility because of the vasoconstrictive effect of norepinephrine on the systemic arterioles[10] and because of the pulmonary vasodilation caused in some patients by tolazoline, a sympatholytic drug.[3–5] However, pulmonary hypertension was not reduced by the administration of hexamethonium,[5,19] blockade of the stellate ganglion bilaterally[20] or bilateral removal of the thoracic sympathetic chain.[3] In our study, the inhibition of two other vasoconstrictors, histamine and prostaglandin, failed to improve the pulmonary hemodynamics in two patients. Histamine stimulates both vasoconstrictor (H_1) and vasodilator (H_2) receptors within the lung. The classic antihistamines such as diphenhydramine compete with histamine for the pulmonary vasoconstrictor sites.[22] The failure of diphenhydramine to decrease pulmonary vascular resistance suggests that accumulation of histamine was not an etiologic factor of the pulmonary hypertension in the two patients studied.

Prostaglandins are not stored in the lung but are rapidly produced in response to a variety of stimuli. Several prostaglandins, including $PGF_{2\alpha}$, are potent pulmonary vasoconstrictors.[12] They are rapidly inactivated in the lung and other tissues, and their synthesis is inhibited by salicylates.[17] Sodium salicylate is a less potent inhibitor of prostaglandin synthesis than aspirin and indomethacin.[17] However, failure of pulmonary arterial pressure and resistance to decrease in two of our patients after intravenous salicylate administration constitutes strong evidence against an etiologic role of the prostaglandins in the disease process. Thus, of the known pulmonary pressor substances examined to date, none has been shown to play a role in primary pulmonary hypertension.

III. *A primary pulmonary hypertensive-like syndrome is known to occur in some patients with lupus erythematosus and Raynaud's disease,*[14–16] and one of our six patients had lupus erythematosus. This relation has led to speculation that pulmonary hypertension may in some way result from abnormal immune mechanisms that affect the pulmonary vessels. In our study and in previous reports, long-term administration of the immunosuppressive agents corticosteroids and azathioprine did not prove effective in decreasing pulmonary arterial pressure.[22,23] However, the acute administration of hydrocortisone did cause a large pulmonary vasodilation in one of five patients, and in the other four, the resistance tended to decrease. The possibility that primary pulmonary hypertension is an autoimmune disease should be evaluated by more specific techniques.

Vasodilator therapy with isoproterenol: None of the pharmacologic maneuvers described provided a good clue to the basic mechanisms in primary pulmonary hypertension, and we could not uncover abnormal pulmonary vasoconstriction. Nevertheless, we considered it worthwhile to determine whether long-term vasodilator therapy would be useful in the disease, even though it might not shed light on the etiology. We elected to utilize isoproterenol for vasodilator therapy, because it has been the most consistently successful of the vasodilators utilized to date and it can be administered sublingually. Isoproterenol is thought to dilate the pulmonary arterioles by increasing intracell cyclic adenosine monophosphate (AMP) and thus it may oppose a variety of vasoconstrictor agents that decrease cyclic AMP, only some of which were considered in the preceding experiments.

Acute intravenous isoproterenol was by far the most effective vasodilator of the pharmacologic agents tested in our study. The drug was not uniformly useful in all patients with primary pulmonary hypertension, and those who will benefit must be selected after measurement of cardiac output, pulmonary arterial pressure and arterial blood gases. Isoproterenol was also found to be useful in two of the three patients who consented to long-term intravenous administration. In the third patient, long-term isoproterenol infusion caused a decrease in the arterial oxygen tension. The microcirculatory picture of the primary pulmonary hypertension is that of hypovascularized areas of lung adjacent to relatively normal areas.[2] Isoproterenol probably dilated only the relatively normal channels remaining in the lung, thereby permitting a further increase in flow in these channels which augmented the ventilation-per-

fusion abnormality and depressed the arterial oxygen tension.

Implications: Patients with primary pulmonary hypertension may have vasoconstriction and irreversible vascular obstruction, or some combination of the two. Two of our six patients were moderately responsive to changes in the inspired oxygen tension and unresponsive to hydrocortisone, whereas a third patient had vasodilation in response to isoproterenol infusion and hydrocortisone, but no response to hypoxia or hyperoxia. Thus, there are large individual variations in the processes that constitute the disease or diseases now called primary pulmonary hypertension. At present the choice of therapeutic agents must be determined empirically. The observation that one patient in our study benefited from long-term isoproterenol therapy represents some progress in a disease that has an extremely poor prognosis when not treated.

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Effect of Afterload Reduction on Plasma Volume During Acute Heart Failure

ROBERT J. HENNING, MD
MAX HARRY WEIL, MD, PhD, FACC

Los Angeles, California

Previous investigations in our unit indicated that acute cardiogenic pulmonary edema is associated not only with an increase in left ventricular end-diastolic pressure and pulmonary arterial wedge pressure but also with a relative increase in colloid osmotic (oncotic) pressure and peripheral hemoglobin concentration. This combination of changes suggested that acute congestive heart failure with pulmonary edema, unlike chronic congestive heart failure, is associated with a contraction of intravascular blood volume. In this study, plasma volume changes were measured before and during the treatment of acute cardiogenic pulmonary edema in 14 patients with arteriosclerotic heart disease. The plasma volume measurement in all 14 patients before the initiation of treatment was either normal or decreased. After treatment with the alpha adrenergic blocking agent phentolamine, the plasma volume increased rather than decreased when measured 4 and 12 hours after the initiation of treatment. During this time colloid osmotic pressure and peripheral hemoglobin concentration progressively decreased. These findings suggest that acute cardiogenic pulmonary edema is associated with the extravasation of large quantities of plasma water from the intravascular compartment into the interstitial compartment and contraction of the intravascular plasma volume. The treatment of acute cardiogenic pulmonary edema is associated with the return of hypo-oncotic fluid from the interstitial compartment back into the intravascular compartment with expansion of plasma volume and reduction of colloid osmotic pressure and hemoglobin concentration.

From the Institute of Critical Care Medicine, the Shock Research Unit and the Department of Medicine, University of Southern California School of Medicine; the Los Angeles County/University of Southern California Medical Center; and the Center for the Critically Ill, Hollywood Presbyterian Medical Center, Los Angeles, California. This study was supported by Research Grant HL-05570 from the National Heart, Lung, and Blood Institute, Grant GM-16462 from the National Institute of General Medical Sciences, Grant RO 1 HS 01474 from the Health Resources Administration, U.S. Public Health Service, Bethesda, Maryland; the Parker B. Francis Foundation, Kansas City, Missouri; and the Cardiopulmonary Laboratory Research Foundation, Los Angeles, California. Manuscript received May 9, 1978; revised manuscript received June 28, 1978, accepted June 28, 1978.

Address for reprints: Robert J. Henning, MD, University of Southern California School of Medicine, Center for the Critically Ill, Hollywood Presbyterian Medical Center, 1300 North Vermont Avenue, Los Angeles, California 90027.

In previous studies[1] of patients with acute cardiogenic pulmonary edema, we investigated the relation between left ventricular filling pressure and colloid osmotic pressure. Left ventricular filling pressure increased in patients with acute cardiogenic pulmonary edema, but the extent to which the increase was related to pulmonary edema was contingent on the difference between colloid osmotic pressure and pulmonary arterial wedge pressure. Acute pulmonary edema appeared when the difference between colloid osmotic pressure and pulmonary arterial wedge pressure, that is, the colloid-hydrostatic pressure gradient, decreased to a level of 5 mm Hg or less.[2]

Typically, both left ventricular filling pressure (pulmonary arterial wedge pressure) and colloid osmotic pressure increased during the acute stage of cardiogenic pulmonary edema.[3] Fluid that was low in colloid content was translocated into the interstitial compartment during acute pulmonary edema, and there was a relative increase in the protein content and colloid osmotic pressure of the residual plasma. The increases in protein concentration and colloid osmotic pressure were associated with an increase in peripheral hemoglobin concentration. This combination of changes suggested that the plasma volume was selectively reduced in patients with acute cardiogenic pulmonary edema. Subsequent

studies demonstrated that acute congestive heart failure, unlike chronic congestive heart failure, is associated with a contraction of the intravascular plasma volume.[4]

In this study, we investigated the possibility that vasodilator treatment of acute cardiogenic pulmonary edema would reverse the colloid-hydrostatic pressure relation and therefore expand the plasma volume. For this purpose we sought a pharmacologic intervention that would reduce both systemic and pulmonary hydrostatic pressures. Phentolamine, an alpha adrenergic receptor blocking agent, was used. It decreases right-sided filling pressure and therefore systemic venous pressure and systemic capillary hydrostatic pressure.[5] By decreasing systemic vascular resistance, phentolamine also decreases left heart filling pressure and therefore pulmonary venous pressure and pulmonary capillary hydrostatic pressure.[6,7]

Methods

Patients: The 14 patients with acute cardiogenic pulmonary edema studied included 8 men and 6 women, aged 52 to 87 years (median 69). All of the patients presented with shortness of breath, bilateral pulmonary rales, cardiomegaly, ventricular (S_3) gallop and chest roentgenograms demonstrating interstitial and alveolar edema of the lungs. In addition, the history and electrocardiograms of all patients indicated arteriosclerotic heart disease.

Measurements: Right atrial, pulmonary arterial and pulmonary wedge pressures were recorded using a balloon-tipped triple lumen catheter (Swan-Ganz thermodilution catheter model 93A-118-7F, Edwards Laboratories, Santa Ana, California). Arterial pressure was monitored after the percutaneous insertion of a Longdwel Teflon® catheter (Becton, Dickinson, and Company, Rutherford, New Jersey) into the femoral artery. Pressures were monitored and recorded on a Hewlett-Packard 7878A recorder utilizing Statham P23Db pressure transducers.[8] Cardiac output was measured with the thermodilution technique[9] every 15 minutes for 2 hours and again at 4, 8 and 12 hours. Five sequential measurements were obtained and the results averaged.

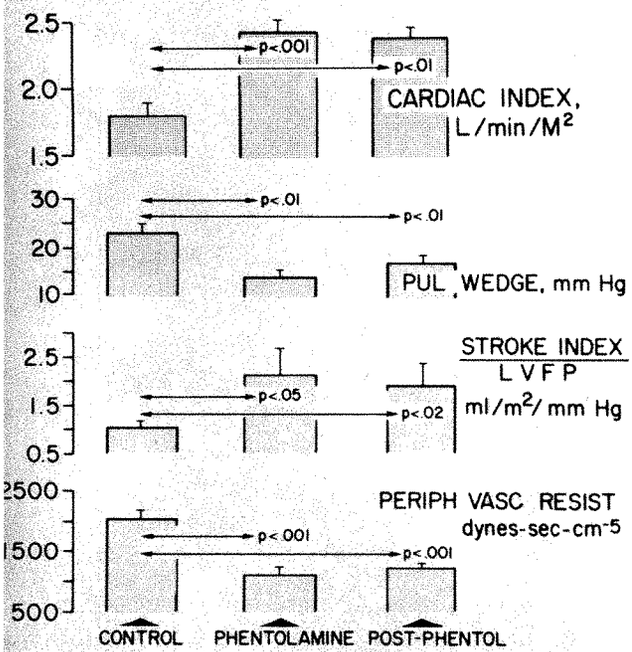


FIGURE 1. Reduction in pulmonary arterial wedge (PUL WEDGE) (left ventricular filling) pressure and peripheral vascular resistance (PERIPH VASC RESIST) with improvement in the cardiac index and the ratio of stroke index to left ventricular filling pressure (LVFP) in response to the administration of phentolamine. Therapeutic effects persist for more than 45 minutes after the discontinuation of phentolamine (POST-PHENTOL). p = probability.

The initial plasma volume was measured after injection of 1 μCi of radioiodinated (iodine-125) human serum albumin (Mallinckrodt Chemical Works, St. Louis, Missouri) into the right atrial port of a flow-directed pulmonary arterial catheter. The amount of radioiodinated human serum albumin injected for subsequent plasma volume determinations was then progressively increased to 2 and 4 μCi. Isotopic activity was determined using 5 ml samples of systemic arterial blood withdrawn 15, 25, 35, 45 and 55 minutes after the injection of radioiodinated (iodine-125) human serum albumin with subsequent extrapolation of the radioactive counts to zero time.[10] Radioactivity was automatically counted on an Ortec scintillation counter, and plasma volume was computed utilizing a Xerox data system Sigma 5 computer. Measurements of plasma volumes were obtained in 13 normal healthy subjects after 3 hours of bed rest. The plasma volume in normal supine subjects ranged from 35 to 50 ml/kg (average 44.6 ± 5.1).[4]

The hemoglobin concentration was determined in duplicate utilizing a co-oximeter (Instrumentation Laboratories, model 182). *Plasma colloid osmotic pressure* was measured using a transducer membrane system with methods previously described.[11] The average colloid osmotic pressure was 25.4 mm Hg in ambulatory patients, decreasing to 21.6 mm Hg when the patients were supine. The mean value of the colloid osmotic pressure for a group of 200 consecutive critically ill patients at the time of admission to our center was 19.1 ± 4 mm Hg.[11]

The fluid intake was closely monitored but tended to be increased because of repetitive thermodilution cardiac output measurements. Urinary output was measured at hourly intervals because each patient had an indwelling urethral catheter.

The initial set of measurements was obtained immediately after the patient was admitted from either the Emergency Department or the general medical or surgical service after the onset of acute cardiogenic pulmonary edema. No diuretic drugs, digitalis glycosides or antihypertensive drugs had been administered. Patients who had evidence of gastrointestinal bleeding or recent myocardial infarction or clinical signs of shock, or who received either colloid or blood transfusions, were excluded from the study.

Phentolamine infusion: Phentolamine was initially infused into the right atrium in amounts of 10 μg/kg per min. The infusion was increased by 10 μg/kg per min every 15 minutes until the systolic blood pressure decreased to 90 mm Hg, the pulse rate exceeded 140 beats/min or a total of 40 μg/kg per min had been administered. The second plasma volume determination was performed 4 hours after the initiation of treatment with phentolamine. Although the administration of phentolamine was followed by an increase in cardiac output and a decrease in filling pressure of the left ventricle, urinary output did not increase significantly.

Furosemide administration: To conform to the protocol approved by the Human Subjects Committee of our institution, furosemide was administered intravenously in doses ranging from 40 to 280 mg (mean 100) after the completion of the initial 4 hours of therapy. The third plasma volume measurement was performed 8 hours after the administration of furosemide.

TABLE I

Results in 14 Patients

Case no.	Hemoglobin (g/dl)			COP (mm Hg)			Plasma Volume (ml/kg)			Fluid Intake (ml/12 hr)	Urinary Output (ml/12 hr)
	Adm	4 hr	12 hr	Adm	4 hr	12 hr	Adm	4 hr	12 hr		
1	13.1	12.9	11.7	23.1	19.4	17.3	41.6	51.8	54.3	1103	2480
2	13.0	10.2	9.6	27.3	20.5	19.1	47.0	66.3	69.3	1940	3063
3	13.9	11.0	9.8	28.4	19.0	18.0	50.0	53.5	61.6	2405	3222
4	12.6	10.4	9.4	28.2	23.7	20.2	27.6	39.6	44.1	1685	2065
5	13.1	11.0	10.2	25.5	21.5	17.9	40.0	44.8	45.8	2895	3984
6	12.0	10.4	9.5	25.5	21.0	18.6	22.2	38.8	45.9	1415	2427
7	15.4	13.3	11.4	27.7	26.2	22.1	33.0	47.0	50.0	3105	3763
8	14.0	10.6	9.3	24.4	17.6	16.3	47.0	53.0	60.0	2760	3418
9	12.3	11.2	10.8	26.3	21.0	18.0	24.0	30.8	34.3	2300	2706
10	13.1	11.3	10.5	20.9	17.8	16.9	34.5	47.5	64.9	1855	2305
11	11.6	10.3	9.7	24.5	22.7	19.4	29.1	35.6	44.2	1103	2083
12	13.8	11.4	10.6	23.7	21.0	16.0	37.3	41.4	45.1	1520	2602
13	13.3	11.3	10.0	22.4	16.9	15.3	32.4	38.9	40.1	1539	2526
14	15.0	13.5	11.7	24.7	17.0	15.0	49.5	52.5	54.5	2067	3035
Mean	13.3	11.3	10.3	25.2	20.4	17.9	36.8	45.8	51.0	1978	2834
±SD	±1.1	±1.1	±0.8	±2.2	±2.7	±2.0	±9.4	±9.2	±10.1	±642	±599
	$P<0.001$	$P<0.001$		$P<0.001$	$P<0.001$		$P<0.001$	$P<0.001$		$P<0.001$	

Adm = on admission; COP = colloid osmotic pressure; P = probability; SD = standard deviation.

Mean values and standard deviations are presented. Student's two tailed t test for paired observations was used for statistical comparison of the data.

Results

Control measurements: Before treatment with afterload reduction, significant increases in peripheral vascular resistance and pulmonary arterial wedge pressure were associated with marked decreases in cardiac index and the ratio of stroke index to left ventricular filling pressure (Fig. 1). The plasma volume averaged 36.8 ± 9.4 ml/kg compared with the normal value of 44.6 ± 5.1 ml/kg (P <0.02) previously found in normal supine subjects (Table I).

Effect of phentolamine: The maximal response to phentolamine was characterized by a decrease in peripheral vascular resistance to 56 percent of the control value and a decrease in pulmonary arterial wedge pressure to 58 percent. Simultaneously, the cardiac index increased to 133 percent of the control value. Four hours after the initiation of treatment with phentolamine, the mean hemoglobin had decreased to 85 percent and the mean colloid osmotic pressure had decreased to 81 percent, but the mean plasma volume had increased to 124 percent of the control value. Figure 2 shows the effects of phentolamine, including a decrease in arterial and pulmonary arterial wedge pressure and

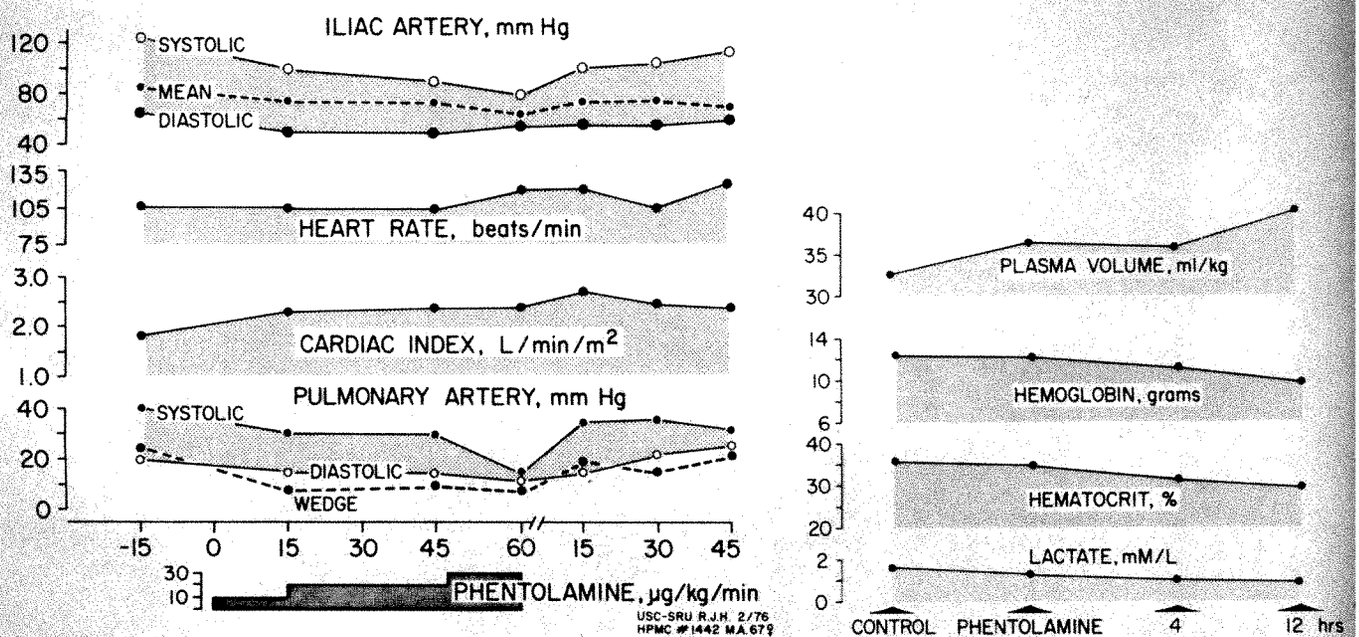


FIGURE 2. Left, reduction in arterial pressure and pulmonary arterial pressure with increase in cardiac index and heart rate during treatment of a 67 year old woman admitted with acute cardiogenic pulmonary edema. **Right,** corresponding changes in plasma volume, hemoglobin, hematocrit and arterial blood lactate in the same patient. L = liter; mM = millimoles.

n increase in cardiac output and plasma volume, in a epresentative case.

Effect of furosemide: After the intravenous injection of furosemide, urinary output increased and exeeded fluid intake by an average of 856 ml at the end f 12 hours. Despite this diuresis, the mean hemoglobin alue decreased further to 77 percent of the control alue, and the mean colloid osmotic pressure decreased o 71 percent of the control value. At the same time, the lasma volume was additionally expanded to an average f 139 percent of the initial value (Table I).

Discussion

Physiologic changes in acute pulmonary edema n congestive heart failure: In the patients studied, cute congestive heart failure with pulmonary edema as characterized by a low cardiac output and an inrease in both pulmonary and systemic venous pres-ures. Accordingly, capillary hydrostatic pressure increased significantly, accounting for the transudation f fluid from the intravascular compartment into the ulmonary and systemic interstitial compartments and he formation of edema. Sympathetic excitation comensates in part for a decrease in cardiac output by timulating myocardial contractility and increasing eart rate and peripheral arterial resistance.[12] The inrease in peripheral vascular resistance also increases he work load on the heart, thereby further increasing ght and left ventricular filling pressures and ultimately oth pulmonary and systemic venous pressures. When he capillary hydrostatic pressure exceeds the colloid smotic pressure (oncotic pressure), the transudation f plasma water into the extravascular compartment ccounts for pulmonary and peripheral edema. As much s one half of the normal plasma volume may rapidly scape into the interstitial spaces and especially into the nterstitium and the alveoli of the lung during acute eart failure.[13,14] Characteristically, this fluid has a rotein concentration that is approximately one half of hat in the plasma.[15,16] On occasion, the reduction in lasma volume is so great that a patient presents with xtreme hypotension due to hypovolemia and requires he administration of fluid (colloid).[17,18]

Effects of afterload reduction therapy: Pharmaologic reduction of afterload is one therapeutic means f interrupting this vicious circle. After the administration of phentolamine, left ventricular filling pressure, ulmonary arterial wedge pressure and pulmonary capillary pressure decreased, and cardiac index increased. When capillary perfusion pressure decreased, the colloid-hydrostatic pressure gradient favored return of hypo-oncotic fluid from the pulmonary and systemic interstitial spaces into the intravascular compartment and accounted for the expansion of the plasma volume and a corresponding decrease in hemoglobin and colloid osmotic pressure.

A decrease in the work load of the heart associated with a decrease in left ventricular filling pressure and an increase in venous capacitance has been observed by Dikshit et al.[19] and others[20,21] after the administration of furosemide to patients with acute heart failure. These changes characteristically precede the onset of diuresis. Consequently, furosemide may also act as a vasoactive agent, independent of its renal effects, and may be potentially useful for interrupting the vicious cycle of cardiac failure, increased afterload and volume depletion.

When plasma volume expands and cardiac output increases during the treatment of acute heart failure, renal blood flow, glomerular filtration and urinary flow increase. This accounts for the apparent paradox of simultaneous expansion of intravascular volume and diuresis. Although the fluid intake was not strictly restricted in this group of patients, the urinary output exceeded the fluid intake by more than 800 ml at the end of 12 hours. This net loss of fluid was nevertheless associated with an increase in intravascular volume. Therefore, renal diuresis does not of itself deplete the intravascular volume because the plasma volume expands rather than contracts after the reversal of acute heart failure with pulmonary edema.

We conclude that improvement in cardiac output with reduction in pulmonary and peripheral vascular resistance during acute cardiogenic pulmonary edema is associated with a net influx of fluid from the interstitial compartment into the intravascular compartment. The treatment of acute heart failure with improvement in ventricular function after vasodilator therapy is associated with expansion of the plasma volume.

Acknowledgment

We gratefully acknowledge the assistance of Sybil Michaels, Chief Laboratory Technologist. We are also grateful to the medical and nursing staffs of the University of Southern California Center for the Critically Ill for referring patients and collaborating in the care of the patients.

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Spectrum of Regular Tachycardias With Wide QRS Complexes In Patients With Accessory Atrioventricular Pathways

)AVID G. BENDITT, MD
:DWARD L. C. PRITCHETT, MD
IOHN J. GALLAGHER, MD

Durham, North Carolina

Reciprocating tachycardia and atrial flutter or fibrillation are the rhythm disorders most frequently documented in patients with accessory atrioventricular (A-V) pathways. Reciprocating tachycardia typically results in a regular tachycardia (140 to 250/min) with a normal QRS pattern, although on occasion bundle branch block aberration occurs. Atrial flutter or fibrillation may result in an irregular ventricular response, with the QRS configuration being normal or exhibiting bundle branch block or various degrees of ventricular preexcitation, or both. Although much less common than either reciprocating tachycardia or atrial flutter/fibrillation, regular tachycardias with a wide QRS complex suggestive of ventricular preexcitation are observed in patients with accessory pathways. Excluding functional or preexisting bundle branch block, several arrhythmias may cause these electrocardiographic findings which may mimic those of ventricular tachycardia.

In the present study a variety of arrhythmias that resulted in tachycardias with a wide QRS complex were examined in 163 patients with accessory pathways who underwent clinical electrophysiologic study for evaluation of recurrent tachyarrhythmias. Twenty-six patients (15 percent) manifested a regular tachycardia with a wide QRS complex suggesting ventricular preexcitation. Atrial flutter with 1:1 anterograde conduction over an accessory pathway (15 of 26 patients, 58 percent) was the most frequent arrhythmia and was usually associated with a heart rate of 240/min or greater (12 of 15 patients). Reciprocating tachycardia with conduction in the anterograde direction over an accessory pathway (antidromic reciprocating tachycardia) occurred in 7 of 26 patients (27 percent), and resulted in a slower ventricular rate than atrial flutter (217 $\pm$ 22 versus 262 $\pm$ 42, $P < 0.01$). Other arrhythmias included reciprocating tachycardia with reentry utilizing a fasciculoventricular or nodoventricular connection (two patients, 8 percent), reciprocating tachycardia with reentry in the atrium or A-V node and anterograde accessory pathway conduction (one patient, 4 percent) and ventricular tachycardia (one patient, 4 percent).

In this study the clinical electrophysiologic diagnostic features of several arrhythmias which cause tachycardias with a wide QRS compex suggesting ventricular preexcitation are outlined. It is apparent that definitive arrhythmia diagnosis during these tachycardias is often complex and usually requires careful study using intracardiac electrode catheter techniques.

From the Division of Cardiology, Duke University Medical Center, Durham, North Carolina. This study was supported in part by grants RR-30 from the General Clinical Research Branch, Division of Health Resources, and HL 15190 from the National Institutes of Health, Bethesda, Maryland. This work was done in part during the tenure of Dr. Benditt is a Fellow of the Medical Research Council of Canada. Dr. Pritchett is the recipient of the National Heart, Lung, and Blood Institute Young Investigator Research Award 1R23 HL 21347-01. This work was done during Dr. Gallagher's tenure is an Established Investigator of the American Heart Association. Manuscript received March 8, 1978; revised manuscript received June 6, 1978, accepted June 7, 1978.

Address for reprints: David G. Benditt, MD, PO Box 341, Mayo Memorial Building, University of Minnesota Medical School, Minneapolis, Minnesota 55455.

Recurrent tachyarrhythmias are a recognized clinical feature in patients with accessory atrioventricular (A-V) pathways.[1–6] In patients with Wolff-Parkinson-White syndrome[1,4,6–10] and in patients with accessory A-V pathways that exhibit conduction block in the anterograde direction,[2,3,5,6] the most frequent rhythm disorder is a paroxysmal regular tachycardia (heart rate 140 to 250/min) with a normal QRS complex or

with a wide QRS complex due to underlying or tachycardia-related bundle branch block. However, atrial fibrillation and atrial flutter also result in clinically important tachycardias in these patients.[6,10] During these atrial arrhythmias the ventricular response is usually irregular and the QRS configuration may be normal or may manifest bundle branch block or variable degrees of ventricular preexcitation.[4,6,10–12] As a result, atrial fibrillation and atrial flutter are a common cause of irregular tachycardias associated with a wide QRS complex in patients with accessory A-V pathways. Occasionally, in the absence of preexisting or tachycardia-related bundle branch block, patients with accessory A-V pathways manifest relatively regular tachycardias with both a 1:1 A-V relation and a wide QRS complex. In a few patients[13–19] these arrhythmias have been shown to be due to antidromic reciprocating tachycardia in which A-V conduction takes place over an accessory pathway, while the ventriculoatrial limb of the reentry circuit is completed by conduction over either the His bundle–A-V node axis or an additional accessory A-V pathway (see section on terminology).[16] Consequently, although relatively rare, antidromic reciprocating tachycardia has become a recognized explanation for the occurrence of regular tachycardias with a wide QRS complex in patients with accessory pathways. However, other arrhythmias (for example, atrial flutter with 1:1 A-V conduction or ventricular tachycardia) may result in a similar electrocardiographic pattern. Therefore, the analysis of regular tachycardias with a wide QRS complex in the presence of an accessory A-V pathway must include a variety of arrhythmias, and specific arrhythmia diagnosis may prove to be complex.

In this report electrocardiographic features and clinical electrophysiologic findings were examined during regular tachycardias with a wide QRS complex in patients with accessory A-V pathways. Patients in whom this electrocardiographic finding was solely the result of preexisting or tachycardia-related bundle branch block were excluded. As a result, a portion of the spectrum of arrhythmias resulting in these regular tachycardias with a wide QRS complex has been examined, and certain electrophysiologic features that may be of value in the differential diagnosis of these arrhythmias have been outlined.

Methods

Patients: Between January 1968 and May 1977, a total of 163 patients with accessory atrioventricular (A-V) pathways were studied in the clinical electrophysiology laboratory at Duke University Medical Center for evaluation of symptomatic recurrent cardiac arrhythmias. During electrophysiologic study, 26 of these patients exhibited a regular tachycardia with a QRS pattern of apparent ventricular preexcitation and a 1:1 A-V relation. The records from these 26 patients form the basis of this report.

All patients (and, where necessary, the patients' parents as well) gave informed consent for these studies. Before the electrophysiologic study a complete physical examination, chest X-ray film and electrocardiogram were obtained for each patient, and except in three patients (Cases 15, 17 and 21) all cardioactive medications were discontinued for more than 48 hours before the study. The latter three patients were studied at a time when therapeutic levels of quinidine sulfate were present.

Procedure: The procedure employed in most patients included in this study was similar to those described previously for the electrophysiologic study of patients with Wolff-Parkinson-White syndrome in this laboratory.[1,20–24] With use of sterile technique and local anesthesia, a no. 6F quadripolar electrode catheter for recording and stimulating and a specially designed 7F bipolar mapping catheter[21,25] (American Catheter Corporation, Vincentown, New Jersey) were introduced percutaneously by way of the right femoral vein and advanced under fluoroscopic control to the apex of the right ventricle and to the right atrium, respectively. A no. 6F tripolar catheter was also introduced percutaneously by way of the right femoral vein and positioned across the tricuspid valve to record a His bundle electrogram. In addition, a no. 6F quadripolar catheter was introduced by way of an antecubital or subclavian vein and advanced to the coronary sinus. As necessary, during the studies the no. 7F mapping catheter was removed and replaced by a no. 6F quadripolar catheter that was placed at the lateral border of the right atrium for recording and stimulating. After introduction of all catheters, 100 units/kg body weight of heparin sodium was given intravenously.

Standard electrocardiographic leads V_1 and II and electrograms from the right ventricle, lateral right atrium, His bundle and proximal and distal coronary sinus were recorded simultaneously and stored on magnetic tape at 3 3/4 inches/sec (9.53 cm/sec). Intracardiac bipolar and unipolar electrograms were recorded at filter frequencies of 50 to 1,000 hertz and 0.1 to 1,000 hertz, respectively. Graphic records were obtained either simultaneously at the time of study or at a later time by playback from tape onto a Mingograph 800-8 channel ink-jet recorder at paper speeds of 200 mm/sec. A simultaneous 10 msec time code was recorded with the data. Stimulation studies were performed using a specially designed stimulator (designed and built by Jackie Kasell, Duke University Department of Medicine) that delivered impulses of 2 msec duration, employing the minimal intensity permitting consistent capture. All electrical equipment was carefully grounded.

Terminology and Differential Diagnosis of Wide QRS Tachycardia in Patients With Accessory A-V Pathways

Wide QRS tachycardia was defined for purposes of this study as a regular tachycardia with a QRS configuration suggesting ventricular preexcitation. The latter was substantiated in all but one patient, by assuring that the QRS configuration during tachycardia was essentially identical with that obtained with atrial pacing near the presumed site of the accessory A-V pathway. In the one patient (Case 26) found to have a left-sided accessory A-V pathway that exhibited conduction block in the anterograde direction, this comparison was not possible.

In the presence of these electrocardiographic findings each of the following pathophysiologic mechanisms, adapted from reports by Fontaine et al.[16] and Frank,[26] was considered. In addition, certain techniques and criteria employed to diagnose various rhythm disorders will be described.

A. Arrhythmias in which the accessory A-V pathway participates in the reentrant circuit, and the QRS configuration suggests block within the specialized cardiac conduction system: Orthodromic reciprocating tachycardia, the arrhythmia most frequently associated with the presence of an accessory A-V pathway, usually manifests as a regular

ichycardia with a narrow QRS complex due to anterograde -V conduction over the A-V node-His-Purkinje system with ntriculoatrial (V-A) conduction by way of an accessory A-V athway. However, in the presence of underlying or tachy-rdia-related bundle branch block, or as a result of antero-ade A-V conduction over a nodoventricular or fasciculo-ntricular connection,[27] a wide QRS complex may result.

The occurrence of orthodromic reciprocating tachycardia as diagnosed with use of the following criteria:

ABLE 1

linical Features in 26 Cases

Case no.	Age (yr) & Sex	Type and Location of Accessory Pathway	Cardiac Abnormality	Wide QRS Tachycardia CL	Wide QRS Tachycardia HR
		A. Antidromic Reciprocating Tachycardia			
1	16M	AAV(LV) + EAVN		210–280	215–286
2	25M	AAV(RV)		300	200
3	47M	AAV(S)		300	200
4	16M	AAV(LV) + EAVN		250	240
		B. Antidromic Reciprocating Tachycardia Utilizing Multiple AAVs			
5	14M	AAV(RV) − AAV(LV) + EAVN	Cardio-myopathy	275	218
6	54M	AAV(S-posterior) + AAV(S-anterior)	BMV	295–330	182–203
7	15M	AAV(RV) + AAV(LV) + EAVN		250–260	230–240
		C. Atrial Flutter With 1:1 Conduction			
8	20M	AAV(S)	Ebstein's, ASD	235	255
9	16M	AAV(LV) + AAV(S)		215	280
10	29M	AAV(S)		320	188
11	13M	AAV(S)		170–200	300–350
12	45F	AAV(RV)	Ebstein's	250	240
13	43M	AAV(S)		200	300
14	61M	AAV(LV)		215	280
15	27F	AAV(S)		340	176*
16	45M	AAV(LV)		215–300	200–280
17	27F	AAV(S)		260	230*
18	38F	AAV(LV)		200	300
19	26M	AAV(RV)	Ebstein's, ASD	220	273
20	56M	AAV(RV)		215–300	200–280
21	12F	AAV(LV)		230	260
22	13F	AAV(S)	BMV	188	320
		D. Reciprocating Tachycardia With Reentry in Atrium or A-V Node			
23	41F	AAV(RV)		275	218
		E. Reciprocating Tachycardia With Reentry Over FV or NV Connection			
24	18F	AAV(S) + NV	Ebstein's, ASD	316	190
25	20M	AAV(RV) + NV	Ebstein's	410	146
		F. Ventricular Tachycardia			
26	42F	AAV(S-left posterior)†		440	136

* In the presence of quinidine.
† Unidirectional retrograde conduction only.
AAV = accessory atrioventricular pathway; ASD = atrial septal efect; BMV = ballooning mitral valve; CL = cycle length (msec); EAVN = enhanced A-V nodal conduction; Ebstein's = Ebstein's anomaly of he tricuspid valve; FV = fasciculoventricular connection; HR = heat ate (beats/min); LV = left ventricle; NV = nodoventricular connection; IV = right ventricle; S = septum.

1. Induction of premature ventricular depolarizations at progressively shorter coupling intervals during tachycardia resulted in preexcitation of the atria with an activation sequence identical to that of the tachycardia, at a time when the His bundle was refractory.[24]

2. The V-A interval increased after onset of functional bundle branch block during reciprocating tachycardia.[23] This finding implicated participation of an accessory A-V pathway on the same side as the bundle branch block, but the absence of this finding did not exclude the presence of a septal accessory pathway.[6]

3. An eccentric retrograde atrial activation sequence occurred during tachycardia (this may not occur with septal pathways).[6,22] Alone, this criterion does not exclude ectopic arrhythmias of atrial origin or arrhythmias due to reentry solely within the atria.

Tachycardias with a wide QRS complex determined to be due to orthodromic reciprocating tachycardia in the presence of tachycardia-related or underlying bundle branch block were excluded from this study because their occurrence is now widely recognized.

B. Arrhythmias in which preexcitation is present and in which the accessory A-V pathway participates in the reentry circuit: Antidromic reciprocating tachycardia, in which A-V conduction takes place by way of an accessory pathway while V-A conduction occurs over the A-V node–His-Purkinje system or by way of additional accessory pathways, or both, are recognized occurrences in patients with accessory A-V pathways capable of conduction in the anterograde direction (that is, Wolff-Parkinson-White Syndrome).[6,15,16,26] The term "antidromic" was first utilized by Fontaine et al.[17] to describe arrhythmias of this type, but its suggestion has been credited to Friedberg.[16] Introduction of this term was considered useful for describing a reciprocating arrhythmia in which conduction moved in the opposite direction to that usually recorded during reciprocating tachycardia (orthodromic tachycardia) in patients with accessory pathways. In addition, it avoided confusion with the existing but now rarely used term "reversed reciprocating tachycardia," which had been used to describe a different arrhythmia.[28,29]

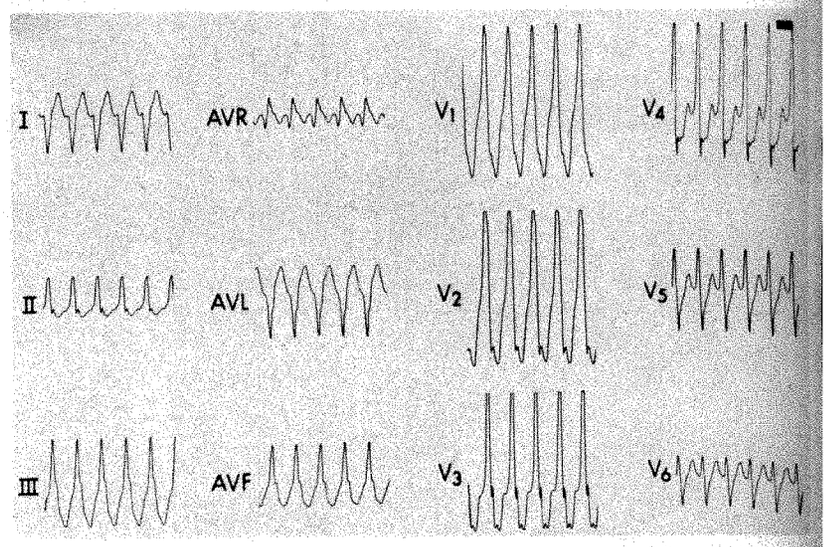
Electrocardiographic and electrophysiologic features suggesting diagnosis of antidromic reciprocating tachycardia include:

1. QRS configuration consistent with maximal ventricular preexcitation.[14,16,26]

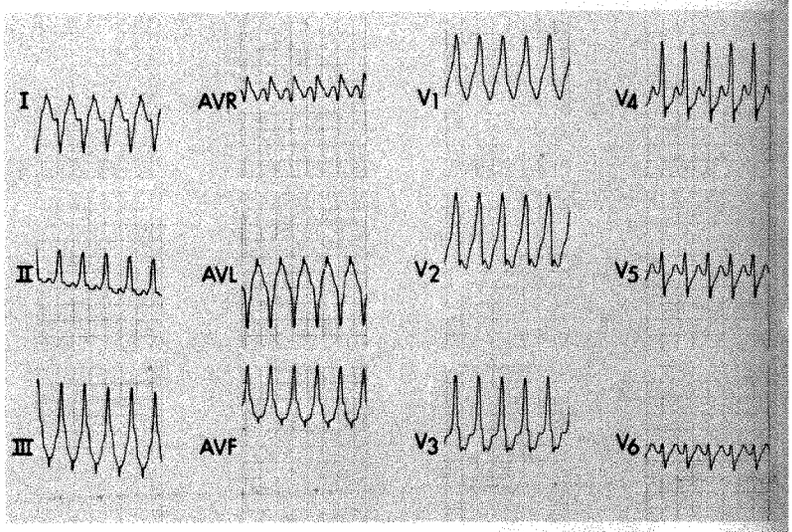
2. Evidence of participation of the ventricles in the reentry pathway. This may be done by demonstrating that premature ventricular depolarization terminates the tachycardia without depolarizing either the His bundle or the atria. Thus reciprocating tachycardia with reentry within the A-V node (see later) or within the atria, or both, is excluded.

3. Evidence that ventricular tachycardia is not present. This may be very difficult to obtain.[26] However, it may be possible to demonstrate that premature ventricular or atrial depolarizations preexcite the atria during tachycardia and advance the tachycardia without disturbing either the timing of *initial* ventricular depolarization of the cycle in which the premature depolarization was placed or the ventricular activation sequence of the tachycardia. Thus autonomous ventricular activity is excluded.

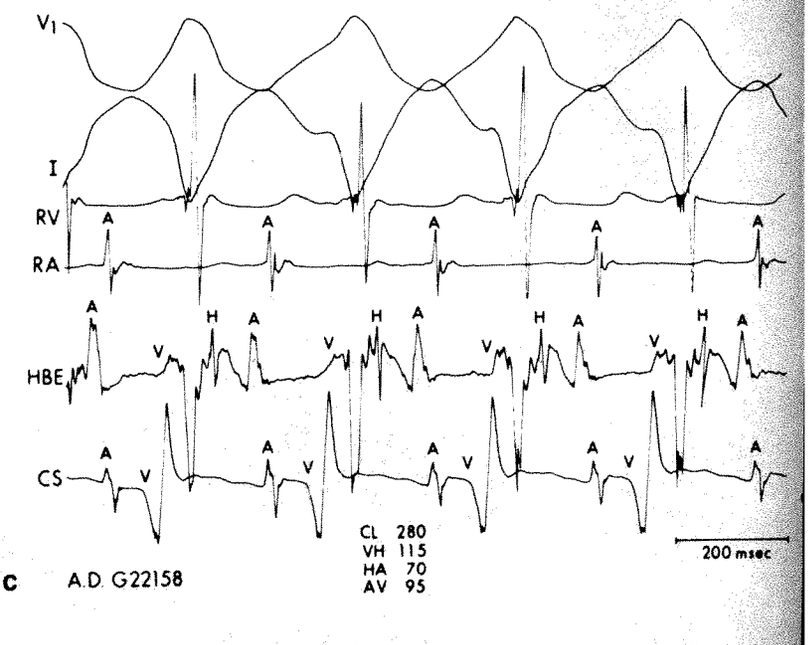
4. Demonstration with ventricular pacing that V-A conduction properties of the A-V node or additional accessory A-V pathways, or both, are capable of sustaining the suspected antidromic reciprocating tachycardia. Fulfillment of this criterion requires the retrograde atrial activation se-



A



B



C

FIGURE 1. Patient 1. **A,** 12 lead electrocardiogram during tachycardia (cycle length 230 msec, 261/min). **B,** 12 lead electrocardiogram during coronary sinus pacing (cycle length 300 msec, pacing rate 200/min) demonstrating maximal preexcitation. The QRS configurations during wide QRS tachycardia **(A)** and during maximal preexcitation are almost identical. **C,** intracavitary recordings during wide QRS tachycardia. Ventricular depolarization (V) is recorded earliest in the coronary sinus (CS) electrogram and is followed by the His bundle deflection (H) and then by the atrial deflection (A) recorded in the His bundle electrogram (HBE). Atrial activity in the high right atrium (RA) and in the coronary sinus (CS) occur later. These findings are consistent with anterograde A-V conduction over a left-sided accessory pathway and retrograde conduction by way of the specialized cardiac conduction system. CL = cycle length; I = lead I of the electrocardiogram; RV = right ventricular apex electrogram.

uence during ventricular pacing to be identical with that corded during the arrhythmia.

C. Arrhythmias in which preexcitation is accentuated, ne accessory A-V pathway is not essential to the mechnism of the arrhythmia and both the accessory pathway nd ventricles may be considered "innocent bystanders": trial flutter with 1:1 A-V conduction, tachycardia due solely reentry within the atria or reciprocating tachycardia with entry within the A-V node (see below) are examples.

Reciprocating tachycardia due to reentry within the A-V ode was diagnosed if atrial activation during the tachycardia curred before or simultaneously with ventricular activation hat is, a V-A interval of 0 msec or less)[30,31] or the following iteria were satisfied[31]:

1. Participation of an accessory A-V pathway in the chycardia was excluded with the criteria noted.

2. Atrial activation sequence during reciprocating chycardia was initiated in the low medial right atrium and as indistinguishable from the normal retrograde conduction quence.[25] This criterion excludes the possibility of reentry ithin the region of the sinus node.

3. Induction of premature ventricular depolarizations at rogressively shorter coupling intervals during the tachyrdia failed to preexcite the atria with the same atrial activation sequence as the tachycardia at a time when the His undle was refractory.[24]

It is recognized that these criteria do not distinguish arythmias caused by reentry within the A-V node from those ue to reentry solely within the low intraatrial septum. owever, attempts to characterize possible atrial participation the reentry circuit by insertion of timed atrial premature polarizations during tachycardia was not carried out rouely in these studies.[32]

D. Arrhythmias due to an ectopic focus or due to entry within the ventricles mimicking ventricular reexcitation: The occurrence of ventricular tachycardia may very difficult to substantiate because retrograde conduction er an accessory A-V pathway may result in a 1:1 A-V relaon.[26]

Enhanced A-V conduction[22,31]: An abnormality of A-V dal conduction was considered present if the following iteria were met at a time when conduction was not occurring er an accessory A-V pathway (for example, after operative lation):

1. The A-H interval in sinus rhythm was less than or equal 60 msec.

2. 1:1 A-V conduction was maintained during right atrial acing at cycle lengths of less than 300 msec (200/min).

3. The maximal A-H interval prolongation associated with 1 A-V conduction during progressively rapid right atrial acing between sinus cycle length and a cycle length of 300 sec (200/min) was equal to or less than 100 msec.

Results

Table I lists the clinical and electrophysiologic findgs in 26 patients with regular wide QRS tachycardias ith 1:1 A-V relation. Twenty-two patients had a single cessory A-V pathway. In two patients the single acssory pathway was associated with enhanced A-V dal conduction, while in the two other patients a sciculoventricular or a nodoventricular connection as also present. One of the latter two patients has reviously been reported on in detail.[33] Four patients ad two accessory A-V pathways, and in two of these atients enhanced A-V nodal conduction was also resent.

Arrhythmias Resulting in Wide QRS Tachycardias

A. Antidromic reciprocating tachycardia: This occurred in seven patients (27 percent) (Cases 1 to 7), with a mean tachycardia cycle length of 277 ± 27.6 msec (heart rate 217 ± 22 beats/min). In four of these patients the V-A limb of the reentry circuit consisted of the A-V node–His Purkinje system; in the other three patients eccentric retrograde atrial activation indicated that one (Cases 5 and 6), or more than one (Case 7) additional A-V pathways participated in the reentry circuit.

The manner in which a diagnosis of antidromic reciprocating tachycardia was established is illustrated by the laboratory findings in Patient 1, in whom the 12 lead electrocardiogram and intracardiac recordings indicated the presence of an accessory A-V pathway in the left lateral A-V groove. During electrophysiologic study a sustained regular tachycardia (cycle length 270 to 300 msec) (Fig. 1A) with a QRS configuration identical to that observed during maximal ventricular preexcitation (coronary sinus pacing, Fig. 1B) was documented, and intracardiac recordings were obtained (Fig. 1C). To permit detailed evaluation, slowing of this tachycardia (cycle length 335 to 440 msec) was accomplished by administration of intravenous procainamide (10 mg/kg) (Fig. 2A).

Diagnosis of antidromic reciprocating tachycardia in which the V-A limb of the reentry circuit consisted of the A-V node–His-Purkinje system was based on the criteria outlined under Terminology and Differential Diagnosis, and is illustrated by the following observations:

1. A premature ventricular depolarization terminated the tachycardia without resulting in either an atrial or a His bundle depolarization (Fig. 2A) thereby implicating the ventricles as essential to the tachycardia circuit.

2. Appropriately timed premature depolarizations induced at the right ventricular apex (RV1–RV2) (Fig. 2B) during tachycardia were capable of preexciting the atria (A_1-A_2) up to 50 msec without having disturbed the timing of depolarization of the base of the left ventricle (LV2). However, subsequent depolarization of the left ventricular base (LV3) occurred earlier than expected, by an amount equivalent to the preexcitation of the atria (50 msec) suggesting that the tachycardia was reset by premature activation of the atria (by way of the A-V node–His-Purkinje system) with subsequent earlier reentry by way of the bypass tract into the left ventricle. Thus, a functional connection between the atria and the base of the left ventricle was substantiated. Had the arrhythmia been ventricular tachycardia it is unlikely that it would have been reset in this manner.

Antidromic reciprocating tachycardia with retrograde conduction over a second accessory pathway located in the septum would also have been consistent with these observations and with the finding that earliest atrial activity was recorded in the His bundle electrogram (Fig. 1C). However, although this possibility could not be absolutely excluded, the observation that a premature ventricular depolarization only terminated the tachycardia at a time when the His bundle spike was no longer recorded (Fig. 2A) suggested that the participation of a septal accessory pathway was unlikely. Retrograde conduction block occurring simultaneously in both the His bundle and in a septal accessory A-V pathway would have been an exceptional coincidence.

Further evidence supporting the occurrence of antidromic reciprocating tachycardia in this case was obtained during electrophysiologic study after successful surgical ablation of a left lateral accessory A-V pathway. During right ventricular pacing, 1:1 V-A conduction was sustained at cycle lengths as short as 220 msec (273/min) with a normal mid-line retrograde

atrial activation sequence. This finding indicated that conduction properties of the A-V node–His-Purkinje system in the retrograde direction were capable of sustaining a rapid antidromic reciprocating tachycardia. In addition, neither antidromic nor orthodromic reciprocating tachycardia could be initiated in the laboratory, and the surface electrocardiogram exhibited a normal QRS configuration suggesting that functional nodoventricular or fasciculoventricular connections were not present.

B. Atrial flutter with 1:1 A-V conduction over an accessory A-V pathway: This occurred in 15 of 26 patients (58 percent) (Cases 8 to 22) and was associated with heart rates greater or equal to 240/min (cycle length 250 msec) in 12 of the 15 patients (80 percent). By way of comparison, similar heart rates were recorded in only 2 of 11 patients (18 percent) with other forms of wide QRS tachycardias. Substantiation of the diagnosis was made in each case by the occurrence of 2:1 A-V block in the accessory pathway, thereby excluding antidromic reciprocating tachycardia, reciprocating tachycardia utilizing a nodoventricular or fasciculo-

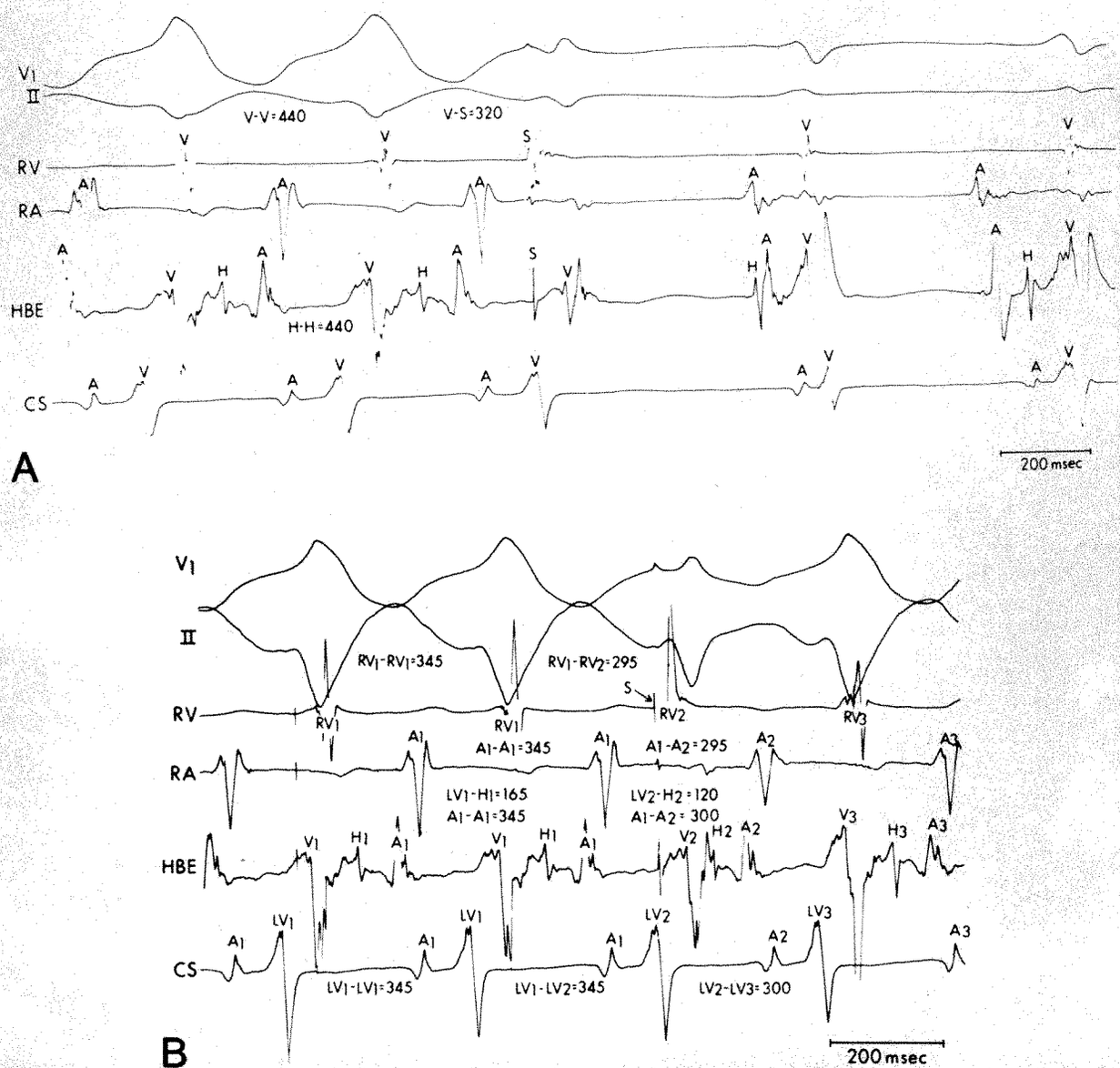


FIGURE 2. Patient 1. **A,** recordings during wide QRS tachycardia after administration of intravenous procainamide to slow the heart rate. A premature ventricular depolarization is initiated by a stimulus (S) at the right ventricular (RV) apex 320 msec after the last ventricular depolarization. The premature ventricular depolarization does not cause depolarization of the His bundle or the atria but terminates the tachycardia. **B,** recordings during wide QRS tachycardia (basic cycle length 345 msec). At the **left,** earliest ventricular activity (LV_1) is recorded in the coronary sinus (CS) electrogram (base of the left ventricle) and later in the His bundle (HBE) and right ventricular (RV) electrograms. Retrograde atrial activation has a mid-line sequence, as in Figures 1C and 2A. A premature ventricular depolarization of the right ventricular apex (RV_2) advances right ventricular depolarization by 50 msec. Similarly H_2 and A_2 are advanced by approximately the same amount, but LV_2 is unaffected, having occurred on time (before RV_2). Subsequently, however, LV_3 is advanced 45 msec with the interval between atrial depolarization in the coronary sinus electrogram (A_2) and ventricular depolarization (LV_3) being unchanged. This finding suggests that earlier left ventricular depolarization (LV_3) occurred as a direct result of atrial preexcitation after RV_2 and thereby supports the diagnosis of antidromic reciprocating tachycardia.

ventricular accessory pathway and ventricular tachycardia.

In two patients (Cases 15 and 17), both with the Wolff-Parkinson-White syndrome and a history of palpitations, documentation of atrial flutter with 1:1 A-V conduction and preexcited QRS complexes was only obtained at a time when both patients were being treated with quinidine. One other patient (Case 21) underwent a brief electrophysiologic study to document the effect of quinidine after an emergency room electrocardiogram documented an episode of wide QRS tachycardia (heart rate 260 beats/min). In this cir-

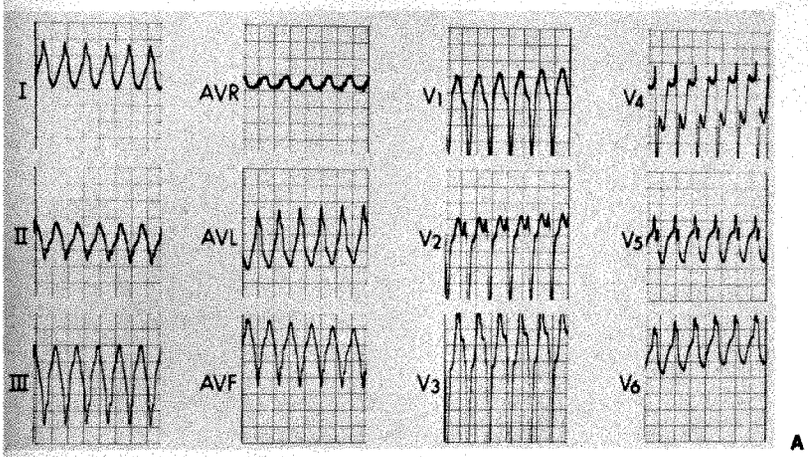


FIGURE 3. Patient 23. **A,** 12 lead electrocardiogram during wide QRS tachycardia (cycle length 275 msec, 218/min), obtained before electrophysiologic study. **B,** intracavitary recordings during tachycardia with a wide QRS configuration similar to that of the tachycardia in **A.** The His bundle deflection (H) occurs within the QRS complex, coincident with depolarization of the right ventricular (RV) apex, suggesting anterograde preexcitation. Atrial activity is recorded earliest in both the His bundle (HBE) and right atrial (RA) electrograms. **C,** intracavitary recordings after spontaneous conversion of wide QRS tachycardia **(B)** to narrow QRS tachycardia. The His bundle spike clearly precedes ventricular depolarization, indicating anterograde A-V conduction over the A-V node–His-Purkinje system. Atrial recordings continue as in **A,** but now the V-A time is short. These findings are most consistent with reciprocating tachycardia with reentry within the atria or A-V node. CL = cycle length; CS = coronary sinus.

cumstance a wide QRS tachycardia with a 1:1 A-V relation occurred that was similar to the patient's original tachycardia but had a slower rate (222 beats/min) because of the presence of quinidine.

C. Reciprocating tachycardia with reentry within the A-V node or atrium and associated with ventricular preexcitation: This arrhythmia was diagnosed in only 1 of the 26 patients (4 percent) (Case 23). This patient was a 41 year old women with a 30 year history of palpitations and documented tachyarrhythmias that on one occasion had been diagnosed as ventricular tachycardia and treated successfully with two 100 mg intravenous bolus injections of lidocaine.

During electrophysiologic study a wide QRS complex tachycardia (210 beats/min) was recorded (Fig. 3, A and B) in which His bundle deflections were displaced into the onset of ventricular depolarization (Fig. 3B) indicating initiation of ventricular activation by conduction over both the A-V node–His bundle and an accessory A-V pathway. Because the earliest atrial activity during this arrhythmia was consistently recorded in the region of the foramen ovale and at the opening of the coronary sinus, the participation of an additional accessory pathway (posterior septal location) in an antidromic reciprocating tachycardia was considered. However, failure of induced ventricular premature depolarizations to preexcite the atria and reset the tachycardia as had been possible in patients with antidromic reciprocating tachycardia made that possibility unlikely. Subsequently, the endocardial surface of the right atrium was mapped intraoperatively, and the earliest atrial activation during the tachycardia was localized to the anterior aspect of the intraatrial septum. Thus, reentry within the atria or an ectopic rhythm initiating within the atria was the most likely mechanism for this patient's arrhythmia.

Typical orthodromic reciprocating tachycardia also occurred in this patient. This tachycardia (180 beats/min) had a narrow QRS complex and utilized an accessory pathway in the right A-V groove as evidenced by an eccentric retrograde atrial activation sequence with the earliest atrial activity recorded on the lateral right atrial wall. The altered atrial activation sequence and a long V-A interval (135 msec) distinguished this tachycardia from either the tachycardia described or an additional tachycardia with a normal QRS complex and a short V-A interval also recorded in this patient (Fig. 3C).

Electrophysiologic study was repeated in this patient after operative ablation of the accessory A-V pathway. Although discontinuous anterograde refractory period curves were demonstrated,[34] repeated attempts failed to precipitate arrhythmias. In addition, this patient has remained free of symptomatic arrhythmias in the 1 year since her operation.

D. Reciprocating tachycardia with reentry utilizing a fasciculoventricular or nodoventricular connection: This mechanism resulted in wide QRS tachycardia in 2 of 26 patients (8 percent) (Cases 24, 25). Electrophysiologic studies in one of these patients (Case 25) have previously been reported,[33] and the analysis of similar cases has been described elsewhere.[17,18] Both patients had Ebstein's anomaly.

E. Ventricular tachycardia with a 1:1 A-V relation: This was documented in only 1 of 26 patients (4 percent) (Case 26). In this case ambulatory electrocardiographic monitoring revealed frequent episodes of regular wide QRS tachycardia (136 beats/min), as well

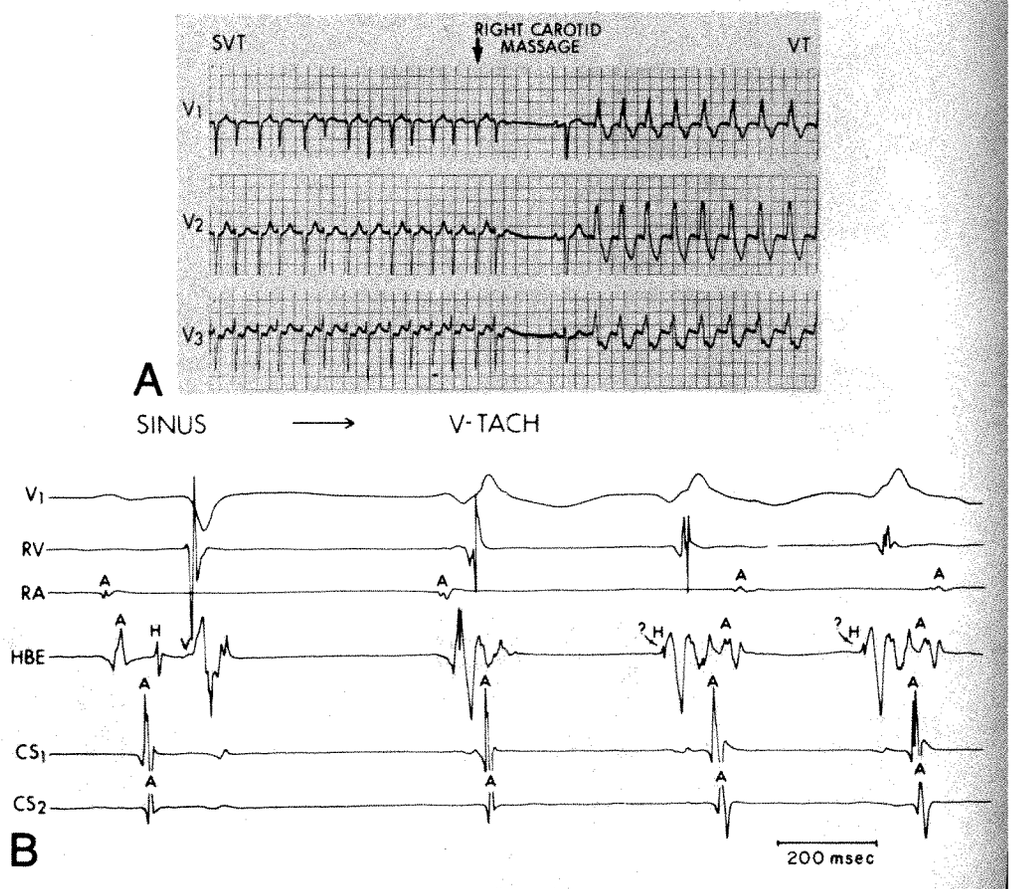


FIGURE 4. Patient 26. **A,** rhythm strip demonstrating termination of irregular narrow QRS tachycardia (SVT) **(left)** by carotid massage, followed by initiation of regular wide QRS tachycardia (VT) (cycle length 440 msec, 136/min). **B,** intracavitary recordings demonstrating spontaneous conversion of sinus rhythm **(left)** to a wide QRS tachycardia (V-TACH) **(right)** similar to that in panel **A.** The His bundle spike (H), clearly recorded during sinus rhythm, is now obscured by initiation of ventricular depolarization. Note 1:1 retrograde (V-A) conduction by way of a left sided accessory pathway (the earliest atrial activation is recorded in coronary sinus (CS_1 and CS_2) electrograms. HBE = His bundle electrogram; RA = right atrial electrogram; RV = right ventricular electrogram.

as numerous single QRS complexes of an identical configuration. During sinus rhythm the 12 lead electrocardiogram showed both a normal QRS configuration and a normal Q-T interval.

During electrophysiologic study the presence of an accessory A-V pathway in the left posterior paraseptal position was documented (see Methods). The participation of this pathway in a somewhat irregular orthodromic reciprocating tachycardia (heart rate 180 to 190 beats/min) (Fig. 4A) was established when spontaneous occurrence of left bundle branch block resulted in 20 to 25 msec prolongation of the V-A interval.[23] In addition, this patient manifested a wide QRS tachycardia (100 to 150 beats/min) that occurred after termination of orthodromic reciprocating tachycardia (Fig. 4A) or spontaneously during sinus rhythm (Fig. 4B). After onset of this tachycardia, His bundle deflections that had been recorded during sinus rhythm became obscured by the initiation of ventricular depolarization. However a 1:1 relation of the atria and ventricles was evident (Fig. 4B).

The differential diagnosis of this tachycardia was simplified by the finding that during right atrial and left atrial (coronary sinus) pacing and during atrial fibrillation, this patient's accessory A-V pathway exhibited conduction block in the anterograde direction. As a result, antidromic reciprocating tachycardia and atrial tachycardia with ventricular preexcitation were excluded. Furthermore, a normal QRS configuration during sinus rhythm and during reciprocating tachycardia at faster heart rates (Fig. 4, A and B) excluded a slower reciprocating tachycardia with aberrant conduction or conduction over a fasciculoventricular connection.

Comparison of Clinical and Electrocardiographic Findings in Arrhythmia Subgroups

Atrial flutter with 1:1 A-V conduction (15 of 26 patients, 58 percent) and antidromic reciprocating tachycardia (7 of 26 patients, 30 percent) were the most frequent arrhythmias resulting in wide QRS tachycardias in this study. Excluding patients who were taking quinidine at the time their tachycardia was studied (Cases 15 and 17), the mean tachycardia cycle length (cycle length 229 ± 36.7 msec, heart rate 262 ± 42/min) was shorter in patients with atrial flutter than in patients with antidromic reciprocating tachycardia (277 ± 27.6 msec, 217 ± 22/min) ($P < 0.01$) (Table I, Groups A and B). This difference is somewhat magnified if the mean cycle length during all forms of reciprocating tachycardia utilizing accessory pathways (Groups A, B and E, Table I) (296 ± 50.7 msec) is compared with that in the group with atrial flutter. However, it is evident from the range of tachycardia cycle lengths observed in each arrhythmia subgroup that cycle length alone cannot be used as an absolute diagnostic feature.

Although all patients with antidromic reciprocating tachycardia were male, the equal distribution of male and female patients in the other arrhythmia subgroups excludes this finding as a helpful differential diagnostic point. Similarly, patient age and location of accessory pathways were not different among the arrhythmia subgroups.

Discussion

Differential diagnosis of wide QRS tachycardia in Wolff-Parkinson-White syndrome: The arrhythmia most frequently noted in patients with accessory A-V pathways is a reciprocating tachycardia in which anterograde A-V conduction takes place by way of the specialized cardiac conduction system, and a reentry circuit is completed by conduction in the V-A direction over one or more accessory A-V pathways.[1,6,8,9,13,26] Consequently, both the sequence of ventricular activation and the QRS configuration in the electrocardiogram are usually normal during this tachycardia (orthodromic reciprocating tachycardia). Furthermore, diagnosis of this arrhythmia is generally straightforward, particularly when it is accompanied by an electrocardiogram during sinus rhythm demonstrating the typical delta wave pattern of ventricular preexcitation (that is, Wolff-Parkinson-White syndrome).[7–9]

Although less common than typical orthodromic reciprocating tachycardia, the occurrence of abnormally widened QRS complexes during paroxysmal arrhythmias in patients with accessory A-V pathways has been noted in several reports.[9,10,15–19,26,35] In particular, differentiation of ventricular tachycardia from supraventricular tachycardias with a wide QRS complex due to ventricular preexcitation has caused considerable difficulty in several instances.[8–11,26,35] In these cases close examination of long rhythm strips during wide QRS tachycardias has often permitted identification of atrial fibrillation or atrial flutter on the basis of an irregular ventricular response or as a result of obvious alterations of QRS configuration suggesting variable degrees of ventricular preexcitation.[8,10,11] Occasionally, however, a relatively regular rhythm with a consistently wide QRS configuration is recorded. The differential diagnosis of the latter arrhythmia is complex, and usually can be resolved only with clinical electrophysiologic study.

Arrhythmias resulting in regular wide QRS tachycardias: Atrial flutter was the most frequent cause of regular wide QRS tachycardia (15 of 26 patients, 58 percent). Although much less frequently reported than either orthodromic reciprocating tachycardia or atrial fibrillation, atrial flutter occurs in approximately 5 percent of patients with Wolff-Parkinson-White syndrome[10] and has frequently been associated with 1:1 A-V conduction.[4] In this circumstance A-V conduction may take place primarily through the accessory A-V pathway, resulting in a preexcited QRS complex, and electrocardiographic findings that suggest a very rapid ventricular tachycardia.[5,10,26] Most likely the striking electrocardiographic appearance of this arrhythmia influenced the frequency with which patients were referred for electrophysiologic evaluation and thereby exaggerated the incidence of atrial flutter with 1:1 A-V conduction in our patient population.

Antidromic reciprocating tachycardia occurred in 7 of 26 patients (27 percent); reciprocating tachycardia with A-V conduction utilizing nodoventricular or fasciculoventricular accessory pathways occurred in 2 other patients. By comparison, Touboul et al.,[18] reviewing their series of unusual reentrant tachycardias in 35 patients with the Wolff-Parkinson-White syndrome, described 4 (11 percent) with regular wide QRS tachy-

cardias. Two of these four patients had typical antidromic reciprocating tachycardia, one had antidromic reciprocating tachycardia with retrograde conduction over a second accessory pathway, and one had manifested reciprocating tachycardia with anterograde A-V conduction over a nodoventricular accessory pathway. Although the report by Touboul et al.[18] did not evaluate other causes of wide QRS tachycardias, the frequency with which reciprocating tachycardia was associated with conduction in the anterograde direction over an accessory pathway was similar to that observed in our patients.

The occurrence of reciprocating tachycardia due to reentry within the A-V node or atrium has been reported in a few patients with the Wolff-Parkinson-White syndrome.[19,36] However, recent studies indicate that many patients originally considered to have reentry within the A-V node as the cause for reciprocating tachycardia in fact have reentrant arrhythmias utilizing accessory A-V pathways that exhibit anterograde block and are therefore concealed.[2,5,37] Thus, exclusion of the participation of a concealed accessory pathway in the tachycardia is essential to the diagnosis of reentry within the A-V node.

Among 139 patients with the Wolff-Parkinson-White syndrome who underwent electrophysiologic study, Wellens[19] noted reciprocating tachycardia due to reentry within the A-V node in 8 and "atrial tachycardia" possibly due to "sinus node reentry" in 3. Thus, in 11 of 139 patients (8 percent), regular reciprocating tachycardias not utilizing a coexisting accessory A-V pathway in the reentry circuit were diagnosed. In our study only one patient (Case 23) had such an arrhythmia, and it resulted in a regular wide QRS tachycardia due to predominant A-V conduction over a right-sided accessory pathway. Presumably the proximity of the accessory pathway to the site of reentry was crucial to the occurrence of preexcitation in our patient. This is the only patient of 163 studied to date at this institution to have thoroughly documented reentry within the A-V node or atrium in the presence of an accessory A-V pathway. Possibly the difference in incidence of reciprocating tachycardia due to reentry within the A-V node or atria in our patients and those described by Wellens[19] lies partially in the criteria used to make this diagnosis. In particular, because the diagnosis is largely one of exclusion (see Definitions), the degree to which participation of additional accessory A-V pathways is searched for[22] and the detail with which the retrograde atrial activation sequence is mapped become important. Thus, differences in laboratory techniques may account for apparent differences in frequency of occurrence of these arrhythmias.

Ventricular tachycardia in patients with the Wolff-Parkinson-White syndrome, although the subject of many case reports,[11,38–42] has rarely been verified. In fact, most reviewers of this topic agreed that alternative explanations, usually atrial fibrillation or flutter with preexcited QRS complexes, were more plausible in almost every case.[8–10,26,35]

Difficulty in documenting the occurrence of ventricular tachycardia in patients with accessory A-V pathways is not surprising because diagnosis of ventricular arrhythmias in the presence of 1:1 association of atria and ventricles (in these cases due to V-A conduction over the accessory A-V pathway) is a complex problem even when intracardiac recording techniques are used.[26] Frank[26] and Puech et al.[43] have indicated certain criteria that may be of value in establishing this diagnosis. To some extent the difficulty in establishing a diagnosis of ventricular tachycardia is reflected by the fact that Wellens[19] documented only one case in a study of 139 patients with the Wolff-Parkinson-White syndrome.[19] and Touboul et al.[18] did not note its occurrence in any of their patients. Similarly, in 163 patients with accessory A-V pathways studied in our laboratory, ventricular tachycardia was proved in only 1 (Case 26).

Clinical implications: It is apparent that in patients with accessory A-V pathways a variety of arrhythmias may result in regular tachycardias with wide QRS complexes. Although the frequency and clinical significance of these tachycardias can be assessed adequately only with use of ambulatory electrocardiographic monitoring, recognition of the underlying rhythm disorders is important because of their tendency to result in rapid heart rates (particularly atrial flutter with 1:1 A-V conduction) and their being easily mistaken for ventricular tachycardia. This study has summarized the complexity of the differential diagnosis of these arrhythmias and has demonstrated the need for careful clinical electrophysiologic evaluation. In addition, certain diagnostic features have been outlined that may be useful during clinical electrophysiologic studies in patients presenting with these electrocardiographic findings.

Acknowledgment

We express our gratitude to the many cardiology fellows who participated in these studies; Laura Cook, RN; Donald Kopp, LPN; the staff of The Electrophysiology Laboratory; Jackie Kasell, electronics consultant; Don Powell and David Huggett, who prepared the illustrations; and Ann Clayton and Brenda Haley, who prepared the manuscript.

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SPECIAL REPORTS

Unstable Angina Pectoris: National Cooperative Study Group To Compare Surgical and Medical Therapy

II. In-Hospital Experience and Initial Follow-Up Results in Patients With One, Two and Three Vessel Disease

University of Alabama Medical Center, Birmingham, Alabama
R. O. RUSSELL, Jr., MD, FACC,* R. E. MORASKI, MD, N. KOUCHOUKOS, MD, FACC, R. KARP, MD, FACC, J. A. MANTLE, MD, FACC, W. J. ROGERS, MD, FACC, C. E. RACKLEY, MD, FACC

University of Chicago—Pritzker School of Medicine, Chicago, Illinois
L. RESNEKOV, MD, FACC,* R. E. FALICOV, MD, FACC, J. AL-SADIR, MD, FACC, H. BROOKS, MD, C. E. ANAGNOSTOPOULOS, MD, FACC, J. LAMBERTI, MD, FACC

Cornell University Medical Center, New York, New York
M. WOLK, MD, FACC,* W. GAY, MD, FACC, T. KILLIP, MD, FACC

Duke University Medical Center, Durham, North Carolina
R. A. ROSATI, MD,* H. N. OLDHAM, Jr., MD, G. S. WAGNER, MD, R. H. PETER, MD, FACC

University of Florida, Gainesville, Florida
C. R. CONTI, MD, FACC,† R. C. CURRY, MD, FACC, G. DAICOFF, MD, FACC

Johns Hopkins University Medical Center, Baltimore, Maryland
L. C. BECKER, MD, FACC,* G. PLOTNICK, MD, FACC, V. L. GOTT, MD, R. K. BRAWLEY, MD, J. S. DONAHOO, MD, R. S. ROSS, MD, FACC

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
A. M. HUTTER, Jr., MD, FACC,* R. W. DeSANCTIS, MD, FACC, H. K. GOLD, MD, FACC, R. C. LEINBACH, MD, FACC, M. J. BUCKLEY, MD, FACC, W. G. AUSTEN, MD, FACC

University of Rochester Medical Center, Rochester, New York
T. L. BIDDLE, MD, FACC,* P. N. YU, MD, FACC, J. A. DeWEESE, MD, FACC

Stanford University Medical Center, Stanford, California
J. SCHROEDER, MD, FACC,* D. STINSON, MD, FACC, J. SILVERMAN, MD

Coordinating Center, Massachusetts General Hospital, Boston, Massachusetts
E. M. KAPLAN, MS, J. P. GILBERT, PhD, A. M. HUTTER, Jr., MD, FACC, J. B. NEWELL

National Heart, Lung, and Blood Institute, Bethesda, Maryland
P. L. FROMMER, MD, FACC, M. B. MOCK, MD, FACC

A prospective randomized study comparing intensive medical therapy with urgent coronary bypass surgery for the acute management of patients with unstable angina pectoris was carried out by nine cooperating medical centers under the auspices of the National Heart, Lung, and Blood Institute. Between 1972 and 1976, a total of 288 patients were entered into the study. All patients had transient S-T or T wave changes, or both, in the electrocardiogram during pain; 90 percent had pain at rest in the hospital, and 76 percent had multivessel coronary disease. The medically and surgically treated patients were comparable with respect to clinical, electrocardiographic and angiographic characteristics and left ventricular function.

During the total study period, the hospital mortality rate was 5 percent in the surgical group and 3 percent in the medical group (difference not significant). The rate of in-hospital myocardial infarction was 17 and 8 percent in the respective groups ($P < 0.05$). In the last 4 years of the study (1973 to 1976), the hospital mortality rate decreased to 3 percent in the surgical group and to 2 percent in the medical group (difference not significant). During the last 3 years of the study (1974 to 1976), the rate of in-hospital myocardial infarction was 13 percent in the surgical group

* Principal Investigator.
† Chairman, Steering Committee.
Address for reprints: Adolph M. Hutter, Jr., MD, Cardiac Unit, Massachusetts General Hospital, 32 Fruit Street, Boston, Massachusetts 02114.

and 10 percent in the medical group (difference not significant). There were no differences in the subsets of patients with one, two or three vessel disease.

In the 1st year after hospital discharge class III or IV angina (New York Heart Association criteria) was more common in medically than in surgically treated patients with one vessel disease (22 percent versus 3 percent, $P < 0.05$), two vessel disease (40 percent versus 13 percent, $P < 0.01$) and three vessel disease (40 percent versus 15 percent, $P < 0.01$). During an average follow-up period of 30 months, 36 percent of the medically treated patients later underwent surgery to relieve unacceptable angina. Late mortality was comparable in the two groups, but the large number of medically treated patients who later underwent surgery prevents definitive conclusions about the relative effect of medical and surgical therapy on long-term mortality. However, the patients who responded to medical therapy did not have a higher late mortality rate than surgical patients.

The results indicate that patients with unstable angina pectoris can be managed acutely with intensive medical therapy, including the administration of propranolol and long-acting nitrates in pharmacologic doses, with adequate control of pain in most patients and no increase in early mortality or myocardial infarction rates. Later, elective surgery can be performed with a low risk and good clinical results if the patient's angina fails to respond to intensive medical therapy.

Unstable angina pectoris is a clinical syndrome that lies between stable angina pectoris and acute myocardial infarction and perhaps sudden death. This syndrome has long been regarded as a premonitory sign of impending acute myocardial infarction.[1,2] Synonyms for unstable angina pectoris have included intermediate coronary syndrome,[3] preinfarction angina,[4] acute coronary insufficiency[5] and coronary failure.[6] Since the introduction of coronary arterial bypass surgery, a controversy has existed about the acute management of unstable angina pectoris. Are patients with this syndrome better managed with emergency coronary bypass surgery or with intensive medical therapy? Uncontrolled studies in recent years describe comparable results with medical[7–10] and surgical therapy.[11–15] Because of differences in clinical definitions and variations in the anatomic extent of coronary disease and left ventricular function, these studies and others have not resolved the controversy.

It was recognized in 1971 that a prospective large scale randomized study comparing these two approaches for the acute management of unstable angina pectoris was necessary to answer the question. Under the auspices of the National Heart, Lung, and Blood Institute, such a study was initiated as a cooperative effort at nine medical centers: The University of Alabama, The University of Chicago, Cornell University, Duke University, The University of Florida, Johns Hopkins University, Massachusetts General Hospital of Harvard University, The University of Rochester and Stanford University. An Advisory Committee to monitor the conduct and the results of the study was established by the National Heart, Lung, and Blood Institute. All data were collated and analyzed by a Coordinating Center established at The Massachusetts General Hospital in Boston, Massachusetts.[16] From 1972 through 1976, a total of 288 patients were prospectively randomized into one group receiving intensive medical therapy and another receiving urgent coronary bypass surgery. This report describes the in-hospital experience of these patients as well as their experience after hospital discharge over an average follow-up period of 30 months. It analyzes the overall medical and surgical groups as well as the subgroups with one, two and three vessel disease.

The purpose of the study was to determine whether unstable angina pectoris is better treated with urgent coronary arterial surgery or vigorous medical management. Intensive medical therapy does not preclude the possibility of later elective surgery if the patient is unacceptably disabled by recurrent or persistent angina. Similarly, urgent surgery does not preclude the subsequent use of medical therapy in patients who have angina after surgery. To assess the relative merits of the two approaches to the patient with unstable angina pectoris, the following end points were assessed: mortality, rate of myocardial infarction, subsequent angina and work status.

Methods

Protocol

Clinical and electrocardiographic criteria: Details of the protocol have been presented previously.[16] In brief, candidates for study were patients with unstable angina pectoris of sufficient severity to warrant admission to an intensive care unit to rule out myocardial infarction. The angina was either of new onset or represented a changing pattern in previously stable angina. The patients had to be less than 70 years of age and, except for coronary artery disease, had to have general health consistent with a further life expectancy of at least 5 years. They must not have had a myocardial infarction within the previous 3 months.

Transient electrocardiographic changes, consisting of S-T segment elevation, S-T depression, T wave changes or a combination of these, had to be documented during episodes of pain. These abnormalities had to revert toward the control pattern after relief of pain and within 24 hours. There had to be no electrocardiographic evidence of an evolving myocardial infarction (that is, pathologic Q waves) during the period of observation. Myocardial infarction had to be ruled out by serial serum enzyme studies obtained on three occasions within the first 24 hours. Finally, patients had to have both surgical and medical options available to them; that is, they must not already have failed an intensive medical program as defined later.

After the clinical and electrocardiographic criteria had been met, the purpose of the proposed studies and the risks and potential benefits of cardiac catheterization, intensive medical

TABLE I

Patient Characteristics

	Medical Group (147 patients)		Surgical Group (141 patients)	
	no.	%	no.	%
Men	121	82	121	86
Previous myocardial infarction*				
None	107	73	92	65
One or more	40	27	49	35
Smoking†	107	73	106	75
Diabetes†	21	14	14	10
Hypertension†	43	29	49	35
Hyperlipidemia†	31	21	28	20
Mean age (yr)	52.7		53	

* Determined from patient's history and electrocardiogram.
† Determined from patient's history.

TABLE II

Clinical Presentation of Patient Population

	Medical Group (147 patients)	Surgical Group (141 patients)
Mean blood pressure (mm Hg) (systolic/diastolic)	132/83	130/83
Mean heart rate (beats/min)	75	75
Angina (% of patients)		
New onset angina	48 (71)	46 (65)
Crescendo angina	52 (76)	54 (76)
Effort	11 (16)	9 (13)
Rest	89 (131)	91 (128)
ECG changes during pain (% of patients)		
Elevated S-T	29 (43)	26 (37)
Depressed S-T	58 (85)	63 (88)
T wave inversion only	13 (19)	11 (16)

Numbers in parentheses indicate number of patients. ECG = electrocardiographic.

therapy and possible coronary bypass surgery were explained to the patient. After informed consent was obtained, selective coronary arteriography, using either the Judkins or the Sones technique, and left ventricular angiography were carried out within 72 hours of admission to the study hospital.

Coronary angiographic and left ventriculographic criteria: To be eligible for randomization, a patient had to have greater than 70 percent luminal diameter narrowing of one, two or three coronary arteries. The distal vessels had to be of adequate size to accept a vein graft and had to be otherwise suitable for surgery. Patients with 70 percent luminal narrowing of one vessel were considered to have second or third vessel involvement if those vessels had greater than 50 percent luminal narrowing. Adequate left ventricular function had to be demonstrated by an ejection fraction of greater than 30 percent and an end-diastolic volume of less than 125 ml/m^2 body surface area.

Patients with greater than 50 percent luminal narrowing of the left main coronary artery were excluded from randomization and were advised to have surgery. Patients with insignificant coronary artery disease or normal coronary arteries, patients with diffuse inoperable disease and patients with inadequate left ventricular function as defined were excluded from randomization and were advised to receive medical therapy. Neither mild nor moderate mitral regurgitation nor the presence of ventricular akinesia or hypokinesia excluded a patient from the study. However, a patient was excluded if preoperative assessment indicated that mitral valve replacement, aneurysmectomy or other cardiac surgical procedures in addition to coronary bypass surgery were needed.

Randomization to medical or surgical treatment: After cardiac catheterization and agreement by both the cardiac surgeon and the cardiologist that the patient was an appropriate candidate for surgery, a tentative surgical date was established before randomization. A randomization card was then pulled from the central supply to determine whether intensive medical or urgent surgical therapy was to be followed. The patient could withdraw from the study at any time, including the period after catheterization or even after randomization. Although some eligible patients were lost to study between the angiographic evaluation and randomization, *no* patient withdrew from the study after randomization.

Patients assigned to surgical treatment had to have coronary bypass surgery within 8 days of admission to the hospital. All patients received appropriate and intensive medical therapy from the time of admission to the hospital until the time of surgery. Patients assigned to medical therapy continued to follow an intensive medical program. The key ingredient of this program was the administration of propranolol and long-acting nitrates in maximal pharmacologic doses as necessary to achieve adequate control of blood pressure and pulse rate throughout a 24 hour period. A systolic blood pressure of 110 to 120 mm Hg and a pulse rate of about 60 beats/min were considered adequate. During evaluation in the coronary care unit, bed rest, appropriate sedation and, when indicated, additional pharmacologic therapy for the control of blood pressure were used. Anticoagulation therapy was left to the discretion of the attending physician.

Analysis of data: Statistical methods used included Student's *t* test to compare the two randomized groups with regard to continuous background variables such as age and blood pressure. Fisher's Exact test was used to compare dichotomous background variables and different outcomes in the hospital and at 1 year and 2 year follow-up intervals; all patients in these comparisons had been equally at risk. When the patients compared had been exposed for unequal lengths of time, methods based on the Mantel-Hanzel statistic were used.[17,18]

Patient Population

From 1972 to December 1976, when patient recruitment ended, 288 patients were randomized. Thus far, the mean follow-up time has been 30 months. Table I summarizes the risk factors of the medical and surgical groups. There were no differences in mean age, proportion of men or percent of patients with previous myocardial infarction. Similarly, the prevalence of smoking, diabetes, hypertension and hyperlipidemia was comparable in the two groups.

Table II summarizes the clinical presentation of ischemic heart disease and the electrocardiographic changes. Mean blood pressure and heart rate at the time of initial evaluation were comparable in the two groups. The unstable angina presented as angina of new onset in about 50 percent of patients in both groups, and in the other patients it presented as a crescendo pattern superimposed on previous chronic angina. The severity of the clinical syndrome is demonstrated by the fact that 90 percent of the patients had angina at rest in the hospital. This occurred with equal frequency among patients with new onset and crescendo angina. The transient

TABLE III

Extent of Coronary Occlusive Disease on Angiography*

	Medical Group (147 patients)		Surgical Group (141 patients)	
	no.	%	no.	%
Single vessel disease	35	24	34	24
RCA	10	7	6	4
LAD	21	14	25	18
LCx	4	3	3	2
Double vessel disease	55	37	47	33
RCA, LAD	22	15	16	11
RCA, LCx	9	6	13	9
LAD, LCx	24	16	18	13
Triple vessel disease	57	39	60	43

* Greater than 70 percent narrowing of at least one vessel, with greater than 50 percent narrowing of second and third vessels.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

TABLE IV

Location of Occlusive Disease in the Left Anterior Descending Coronary Artery

	Medical Group (147 patients)		Surgical Group (141 patients)	
	no.	%	no.	%
Proximal*	47	32	41	29
Distal	36	24	36	26
Proximal and distal	19	13	23	16
None	45	31	41	29

* Proximal to first septal perforating branch.

electrocardiographic changes during pain were also comparable in the medical and surgical groups.

The extent of coronary occlusive disease is summarized in Table III. Single vessel disease was present in 24 percent of patients in both the medical and surgical groups. Double vessel disease was present in 37 percent of patients in the medical group and 33 percent of patients in the surgical group. Three vessel disease was present in 39 percent of patients in the medical group and 43 percent of patients in the surgical group. None of these differences was significant.

The locations of obstruction in the left anterior descending coronary artery are indicated in Table IV. If significant occlusion, defined as greater than 70 percent luminal narrowing, was present, a second lesion was considered significant if it had greater than 50 percent luminal narrowing. The distribution of the obstructive lesions in the left anterior descending artery was comparable in the medical and surgical groups.

TABLE V

Left Ventricular Hemodynamics

	Medical Group (147 patients)		Surgical Group (141 patients)	
	no.	%	no.	%
Left ventricular end-diastolic pressure (mm Hg)				
0–7	34	23	39	28
8–12	50	34	51	36
13–30	38	26	34	24
Unknown	25	17	17	12
Left ventricular end-diastolic volume (ml)				
<123	34	23	30	21
124–145	22	15	27	19
146–176	26	18	18	13
>176	21	14	21	15
Unknown	44	30	45	32
Left ventricular ejection fraction (%)				
30–49	34	23	32	23
50–59	32	22	34	24
60–69	28	19	27	19
70–85	31	21	31	22
Unknown	22	15	17	12

Table V lists the left ventricular hemodynamic data. There was no difference in left ventricular end-diastolic pressure, end-diastolic volume index or ejection fraction between the medical and surgical groups.

Comparison of first and second halves of study: The characteristics of the medical and surgical groups described were analyzed separately for medically treated patients randomized in the first and second halves of the study, and the same analysis was carried out for surgically treated patients. There were no differences in the two groups during the two time periods. Similar analysis of the subgroups of medically and surgically treated patients with one, two and three vessel disease revealed no differences.

Results

Mortality: Figure 1 depicts in-hospital and late mortality for patients with one, two and three vessel disease and for the total medical and surgical groups.

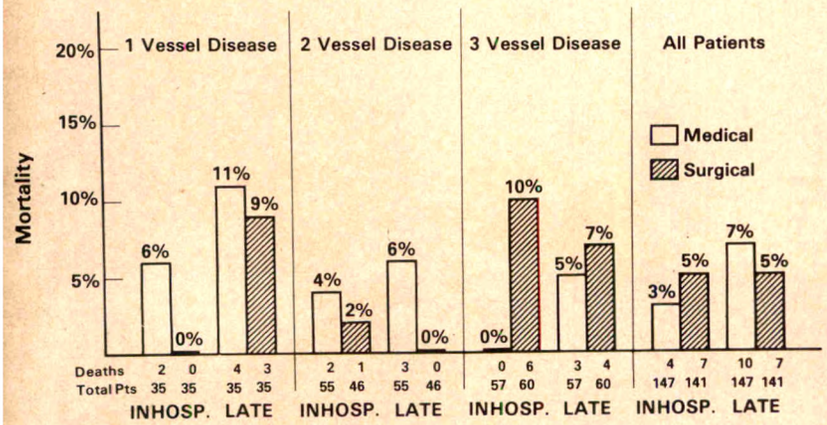


FIGURE 1. In-hospital (INHOSP.) and late mortality rates of medically and surgically treated patients (Pts).

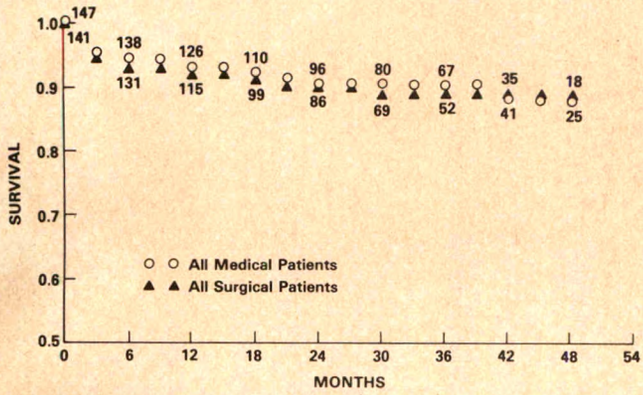


FIGURE 2. Survival of patients randomized to medical and surgical therapy. Numbers above and below curves indicate patients at risk.

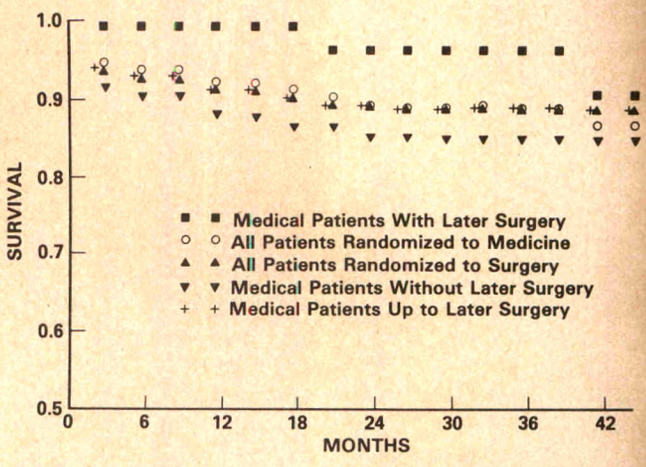


FIGURE 3. Survival of patients analyzed with different techniques (see text).

For patients with one vessel disease, the in-hospital mortality rate was 6 percent in the medical and 0 percent in the surgical group, and for patients with three vessel disease the rate was 0 percent in the medical and 10 percent in the surgical group. However, these differences were not significant. The overall in-hospital mortality rate of 3 percent for medical and 5 percent for surgical treatment was comparable. After a mean follow-up period of 30 months, the late mortality was also comparable for medically and surgically treated patients with one, two and three vessel disease and for the total medical and surgical groups.

Figure 2 shows that the survival curves for patients assigned to surgical and medical therapy did not differ statistically. The 1 year survival rate was 93 percent for the medical and 92 percent for the surgical group; at 2 years, the respective estimated survival rates were 91 and 90 percent. Thirty-six percent of the medically treated patients later had elective surgery for unacceptable angina. To deal with this problem, surgical survival was compared with medical survival analyzed with various techniques. Figure 3 summarizes this analysis. The open circles indicate the survival rate of all 147 patients randomized to medical therapy as shown in Figure 2. The plus signs show the survival rate of all 147 medically treated patients up to the point of later elective surgery, with those patients who later underwent surgery being considered lost to follow-up at the time of surgery. The closed inverted triangles show the survival rates of the 94 medically treated patients who did not undergo later surgery. The closed squares depict the survival of the 53 medically treated patients who later underwent surgery for unacceptable angina despite intensive medical therapy. There was no significant difference between any of these four medical survival curves and the surgical curve indicated by the closed upright triangles.

Myocardial infarction: To analyze the end points of myocardial infarction, angina and work status, all patients up to the point of death or later surgery were included in the medical group, and those patients who later underwent surgery were considered lost to follow-up thereafter. To avoid considering patients at more than one end point, only nonfatal myocardial infarctions were considered in this analysis. An infarction was considered nonfatal if the patient survived at least 30 days after the infarction. A patient who died within 30 days of infarction was classified as a death. Figure 4

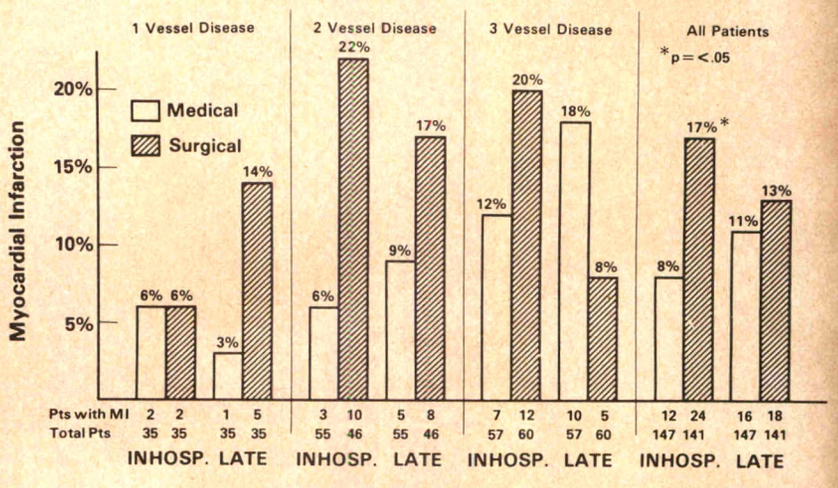


FIGURE 4. In-hospital (INHOSP.) and late nonfatal myocardial infarction (MI) rates in patients (Pts) randomized to medical and surgical treatment. p = probability.

indicates the incidence of myocardial infarction as indicated by the development of new pathologic Q waves in the electrocardiogram, both in the hospital and late. The in-hospital rate of myocardial infarction was comparable in medically and surgically treated patients with one vessel disease but higher in surgically treated patients with two and three vessel disease; none of these differences was statistically significant. However, the 17 percent in-hospital rate of myocardial infarction for all surgically treated patients was significantly higher than the 8 percent rate for all medically treated patients ($P < 0.05$).

The rate of late myocardial infarction was higher in the surgically than in the medically treated patients with one and two vessel disease but higher in the medically treated patients with three vessel disease. None of these differences was statistically significant. The overall rates of late infarction of 11 percent in medically treated and 13 percent in surgically treated patients were comparable.

Angina pectoris: Figure 5 depicts the percent of patients who had class III or IV angina (New York Heart Association functional classification)[19] during the 1st and 2nd years of follow-up. Severe angina was significantly more common in medically treated patients with one ($P < 0.05$), two ($P < 0.01$) and three ($P < 0.01$) vessel disease in the 1st year. Forty percent of the medically treated patients with multivessel disease had class III or IV angina compared with 14 percent of the surgically treated patients ($P < 0.01$). The incidence of severe angina was also significantly higher during the 2nd year in medically treated patients with single vessel disease but not in medically treated patients with two and three vessel disease, probably because patients with more extensive coronary artery disease were far more likely than those with single vessel disease to undergo later surgery for the relief of angina.

Later surgery for persistent angina in medical group: Fifty-three medically treated patients (36 percent) later underwent surgery for relief of angina that was unacceptable in terms of the patient's life style. Unacceptable angina occurred in the medical group at a fairly steady rate (Fig. 6). Only 3 percent required surgery during the initial hospitalization, but 13 percent resorted to surgery by 6 months, 19 percent by 1 year and 31 percent by 2 years. Data on the medically treated patients who later underwent surgery were analyzed in an attempt to find characteristics that might predict whether a patient would require surgery for relief of unacceptable angina. No predictive correlation could be found on the basis of type of angina (new onset or crescendo), the severity or duration of pain or type of electrocardiographic changes during pain. The only feature that correlated with a subsequent need for surgery was the anatomic extent of disease. In the medical group, 20 percent of patients with one, 33 percent of patients with two and 49 percent of patients with three vessel disease later underwent surgery, a highly significant relation. Among the medically treated patients who later underwent surgery, angina after surgery was less severe in 78 percent, more severe in 2 percent and did not change in 20 percent.

A second operation for unacceptable angina was performed in 5 surgically treated patients: 2 of 35 patients with one vessel disease, 2 of 46 with two vessel disease and 1 of 60 with three vessel disease.

Work status: Figure 7 shows the percent of patients working full- or part-time at 1 and 2 years. A higher percentage of medical than surgical patients with single vessel disease are working during the 1st year. However, this and the other differences are not statistically significant. About 70 percent of patients with one and two vessel disease and 50 percent of patients with three vessel disease in both the medical and surgical groups have returned to work during the first 2 years.

Yearly experience in mortality and myocardial infarction rates: Because surgical management has improved in centers throughout the country during the span of this study (1972 through 1976), the rates of in-hospital mortality and myocardial infarction were analyzed on a yearly basis for both surgical and medical groups. In 1972, the 1st year of the study, 3 of 14 surgi-

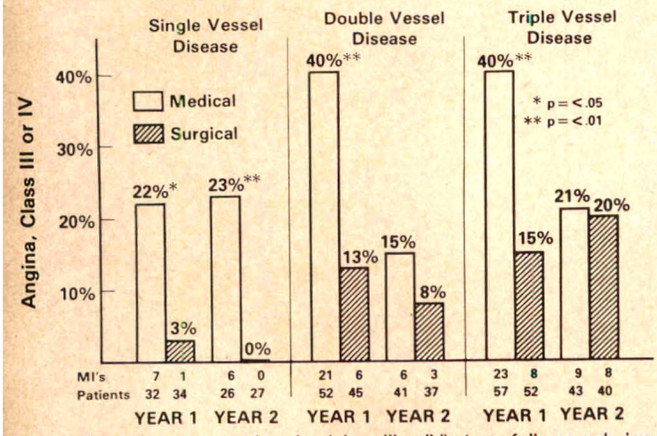


FIGURE 5. Worst degree of angina (class III or IV) at any follow-up during the 1st and 2nd years after randomization. MI's = myocardial infarctions; p = probability.

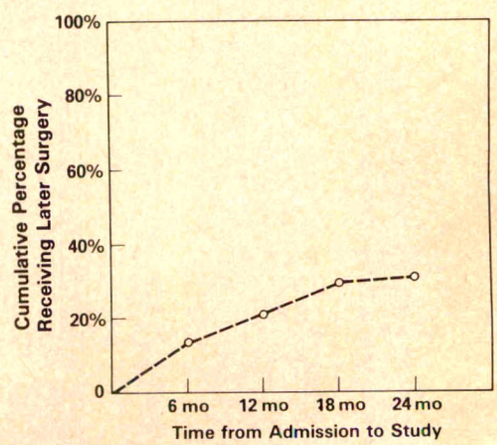


FIGURE 6. Estimated cumulative occurrence of later surgery for relief of angina in patients randomized to medical therapy. mo = months.

cally treated patients (21 percent) died in the hospital (Fig. 8). In contrast, from 1973 through 1976, 4 of 127 surgically treated patients (3 percent) died. Two of 18 medically treated patients (11 percent) died in the hospital in 1972. However, from 1973 through 1976, only 2 of 129 medically treated patients (2 percent) died. Thus, from 1973 through 1976 the in-hospital mortality rate was 3 percent for surgical and 2 percent for medical therapy.

The in-hospital rate of myocardial infarction, as diagnosed from new Q waves, was 25 percent (12 of 48) in surgically treated patients in the first 2 years of the study, 1972 and 1973 (Fig. 9). From 1974 through 1976, 12 of 93 surgically treated patients (13 percent) had an in-hospital infarction. The rate of in-hospital myocardial infarction among medically treated patients was 10 percent (12 of 124 patients) during the first 4 years of the study; the annual rate during this period was relatively constant. In 1976 no in-hospital infarction occurred among 23 medically treated patients. The reason for this decrease is not known, and it may have been due to chance.

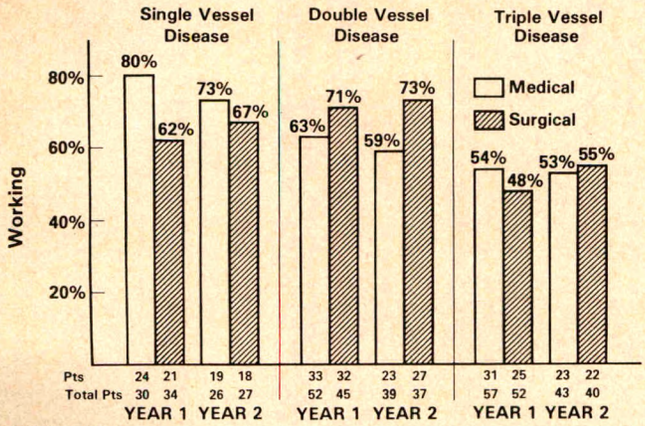


FIGURE 7. Percent of patients (Pts) working full- and part-time at 1st and 2nd year follow-ups.

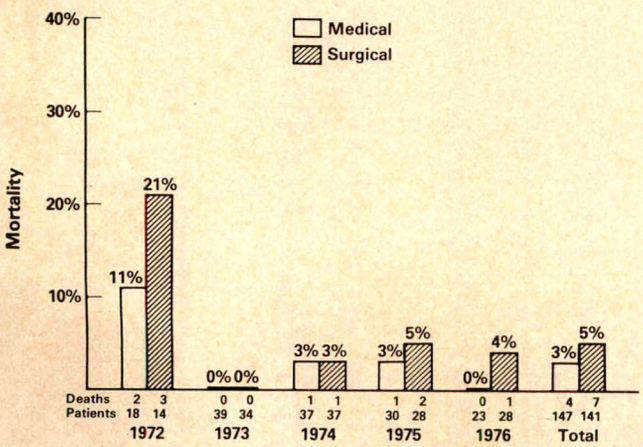


FIGURE 8. In-hospital mortality rates classified by the patient's year of entry into the study.

Complete revascularization attempts: Patients who underwent attempted complete and incomplete (because of unsuitable distal vessels) revascularization were compared. Of the patients with attempted incomplete revascularization, 64 percent had three vessel disease and 34 percent had two vessel disease involving the left circumflex artery. Thus, 98 percent of the patients with attempted incomplete revascularization had multivessel disease involving the circumflex artery. In the total surgical experience, 91 percent of the diseased left anterior descending vessels, 83 percent of the diseased right coronary arteries and 60 percent of the diseased circumflex arteries were bypassed.

Because patients with single vessel disease would be disproportionately represented in the group with attempted complete revascularization, only patients with two and three vessel disease were considered in comparing the results of patients with attempted complete and incomplete revascularization. Of the 50 patients with attempted incomplete revascularization, 6 (12 percent) died and 10 (20 percent) had a nonfatal myocardial infarction in the hospital. Of the 56 patients with attempted complete revascularization, 1 (2 percent) died and 12 (21 percent) had a nonfatal myocardial infarction in the hospital. Neither difference was significant. Angina, class III or IV, occurred during the 1st year of follow-up with comparable frequency in patients with attempted incomplete (8 of 42; 19 percent) and complete (6 of 55; 11 percent) revascularization. Work status was also comparable in the two groups.

Analysis of the location of myocardial infarction in surgically treated patients revealed that 19 of the in-hospital and 10 of the late myocardial infarctions occurred in the area perfused by a grafted vessel. Only four of the in-hospital infarctions and two of the late infarctions occurred in the area perfused by a nongrafted diseased vessel. In three patients, the location of the myocardial infarction could not be determined. Thus,

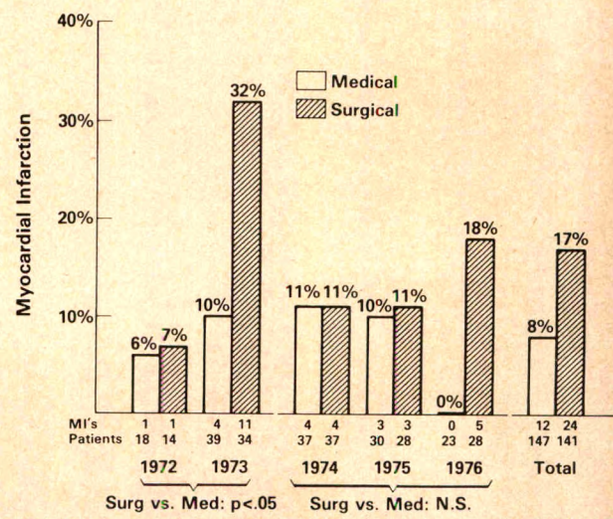


FIGURE 9. In-hospital myocardial infarction (MI) rates classified by the patient's year of entry into the study. Med = medical; N.S. = not significant; p = probability; Surg = surgical.

TABLE VI

Summary of Deaths

	Mechanism	Month of Occurrence
Surgical Group		
Single vessel disease		
1. RCA	Suicide	3
2. LAD	Suicide	9
3. LAD	Sudden*	20
Double vessel disease		
4. RCA, LCx	MI	≤1
Triple vessel disease		
5. RCA, LAD, LCx	Hemorrhage (infected wound)	≤1
6. RCA, LAD, LCx	OR (MI)	≤1
7. RCA, LAD, LCx	OR (VT)	≤1
8. RCA, LAD, LCx	OR	≤1
9. RCA, LAD, LCx	MI	≤1
10. RCA, LAD, LCx	Hemorrhage (infected wound)	≤1
11. RCA, LAD, LCx	Congestive failure	2
12. RCA, LAD, LCx	MI	3
13. RCA, LAD, LCx	MI	17
14. RCA, LAD, LCx	Sudden*	27
Medical Group		
Single vessel disease		
1. RCA	MI	≤1
2. LAD	MI	≤1
3. LCx	Bowel obstruction (cancer)	2†
4. LAD	Unknown	5
5. LAD	Aortic dissection	15
6. RCA	Cancer	21
Double vessel disease		
7. LAD, LCx	MI	≤1
8. LAD, LCx	Suicide	≤1
9. RCA, LAD	Sudden*	2
10. RCA, LCx	Congestive heart failure	11
Triple vessel disease		
11. RCA, LAD, LCx	Sudden*	2
12. RCA, LAD, LCx	MI	10
Medical therapy with later surgery		
1. RCA, LCx	OR (MI)	18‡
2. RCA, LAD, LCx	Unwitnessed	41§

* Within 2 hours of symptoms.
† Cancer diagnosed after randomization.
‡ At later surgery.
§ 22 months after later surgery.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; OR = in operating room; ≤1 month = in the hospital; RCA = right coronary artery; VT = ventricular tachycardia.

perioperative myocardial infarction occurred more frequently in the area perfused by grafted vessels than by nongrafted but diseased vessels.

Deaths: Table VI summarizes the data on all of the patients who died. Six medically treated patients with single vessel disease died, including three patients who did not have left anterior descending artery disease. However, only two of the deaths were definitely related to coronary artery disease; three were related to other disease processes, and the cause of one death is not known. Only one of the three deaths in surgically treated patients with single vessel disease was sudden and therefore presumed to be caused by a cardiac event. The cause of death in medically treated patients with multivessel disease who did not undergo later surgery was a cardiac event in five patients and suicide in one. All of the deaths in surgically treated patients with multivessel disease were caused by a cardiac event or a complication of surgery. Two medically treated patients who later underwent surgery died. One death was caused by a myocardial infarction at surgery, and the cause of the other death, 22 months after surgery, is not known.

Discussion

Comparison of medical and surgical results: The 288 patients randomized in this national cooperative study had severe unstable angina. Ninety percent had pain at rest in the hospital, and all had documented transient S-T or T wave changes during pain. Multivessel coronary disease was present in 76 percent.

This study confirms that urgent coronary bypass surgery can be performed in patients with unstable angina with reasonable safety and good clinical results. With improved surgical techniques, the in-hospital mortality rate among surgically treated patients decreased to 3 percent from 1973 through 1976, and the in-hospital rate of myocardial infarction decreased to 13 percent from 1974 through 1976.

Intensive medical therapy proved an acceptable alternative to urgent cardiac surgery because the rates of early mortality and myocardial infarction were lower than once thought.[7–10] The in-hospital mortality rate among medically treated patients decreased to 2 percent from 1973 through 1976, and the rate of in-hospital myocardial infarction averaged 10 percent.

After a mean follow-up period of 30 months, medical therapy has been effective in the majority of patients. However, significantly more medically than surgically treated patients have had class III or IV angina, and 36 percent of the medically treated patients have thus far had later surgery for relief of unacceptable angina. Patients with more extensive coronary artery disease are more likely to require later surgery for unacceptable angina. Work status appears comparable in the surgical and medical groups.

The problem of later surgery for angina unresponsive to medical treatment: The high proportion of medically treated patients who undergo later surgery for relief of unacceptable angina poses difficulties in interpreting the survival curves shown in Figure 2. A true comparison of long-term mortality in the groups randomized to medical and surgical treatment would require that no medical patient be allowed to receive later surgery. However, principles of ethical medical practice prohibit withholding surgery from patients who continue to have unacceptable angina while receiving maximal medical treatment.

To deal with this problem, survival in the medical group was analyzed with various techniques (Fig. 3), each of which presents its own difficulty. The curve for all 147 patients randomized to medical therapy includes the 53 patients (36 percent) who later underwent elective surgery, and therefore this curve does not truly reflect mortality from medical therapy alone. The curve for the 147 medically treated patients up to the point

of later elective surgery, with the patients who later underwent surgery considered lost to follow-up at the time of that surgery, excludes an unknown proportion of patients who might have died had they not received surgery for unacceptable angina. The curve of the 94 medically treated patients who did not undergo later surgery excludes the 53 patients with intractable angina who might have been at greater risk for subsequent death. The curve of the 53 medically treated patients who later underwent surgery for unacceptable angina despite intensive medical therapy includes all the patients who received both medical and later elective surgical therapy. There is no significant difference between any of these four survival curves for medically treated patients and the survival curve for surgically treated patients. However, we do not know what would have happened to the medically treated patients who later underwent surgery if they had not undergone surgery. Therefore, a definitive statement about the effect on long-term mortality of exclusive medical versus surgical therapy cannot be made at this time. However, the survival curve of the patients who were treated with intensive medical therapy initially and who later underwent surgery for angina unresponsive to medical treatment was at least as good as that of the patients who underwent urgent surgery shortly after admission.

The term *crossover,* which has sometimes been used to describe medically treated patients who later undergo surgery, is probably inappropriate in this study because patients were not randomized into purely medical or purely surgical groups. The study compared a regimen of urgent surgery with a regimen of intensive medical management followed by elective surgery if chronic symptoms warranted it. Thus, there were no crossovers between the two regimens. Furthermore, the study was not designed to compare long-term mortality in purely medical versus surgical treatment, but rather to determine how to manage acutely patients with unstable angina pectoris and assess the long-term results of the two regimens.

Patients with left main coronary artery disease were not evaluated in this study because they were advised to have surgery. Recently published data from the Veterans Administration Cooperative Study on Stable Angina[20] indicate that symptomatic patients with a greater than 50 percent obstructive lesion of the left main coronary artery have a significantly higher rate of survival with coronary bypass surgery than with medical therapy. Therefore it seems reasonable to advise early bypass surgery for patients with left main coronary artery disease and unstable angina pectoris.

Reasons for improved survival in medically treated patients: The rate of survival in the medical group was higher than previously reported for patients with this syndrome; it was 93 percent at 1 year and 91 percent at 2 years. A higher mortality rate for unstable angina pectoris was reported in studies published in 1972 and 1973.[7–10] In a total of 457 patients with unstable angina pectoris at four university centers, the 1 year mortality rate was 15.7 percent. The medical survival rate was analyzed by considering the patients initially assigned to medical therapy, by considering the medically treated patients up to the time of later surgery and by considering only those patients who did not have later surgery; each of these analyses revealed a medical survival rate that was higher than the rate reported in previous studies. The cooperative study on stable angina from the Veterans Administration Group[21] also demonstrated a survival rate in medically treated patients that was higher than the rate reported in previous studies. The 2 year survival rate for single vessel disease was 94 percent; for double vessel disease, 90 percent; and for triple vessel disease, 88 percent. In contrast, Bruschke et al.[22,23] reported that the 2 year survival rate for single vessel disease was 95 percent; for double vessel disease, 80 percent; and for triple vessel disease, 66 percent. Webster et al.[24] and Oberman et al.[25] reported similar findings. Several factors may have contributed to the improved results of medical therapy in our study. First, the early reports on unstable angina did not describe in detail the anatomic extent of coronary artery disease or left ventricular function. Our study provided coronary angiographic data on all patients and excluded patients with left main coronary artery disease or an ejection fraction of less than 30 percent. Thus, it is difficult to compare the patients with unstable angina pectoris in the various studies. Comparing patients with stable angina is more valid because the medical survival rate reported by the Veterans Administration group for patients with stable angina as well as the rates reported in earlier studies were determined separately for patients with one, two and three vessel disease. However, the data on left ventricular function are not sufficient in these studies to allow comparison of this important factor.

A reasonable and perhaps likely explanation for the apparent improvement in medical survival is that medical therapy has improved in recent years. In the late 1960s and early 1970s, the concept of 24 hour coverage with pharmacologic doses of beta adrenergic blocking agents and long-acting nitrates was not widely accepted. Goldstein and Epstein,[26] in an editorial written in 1973 on the role of nitrates in the treatment of angina pectoris, concluded that it is "probably premature to arrive at a final judgment concerning the therapeutic value of oral nitrates on the basis of the data currently available." Since then, a number of studies have greatly improved our understanding of the duration of action of the various forms of nitrates as indicated by their effect on hemodynamic function. Using fixed doses, Sweatman et al.[27] showed that sublingual isosorbide dinitrate caused hemodynamic changes lasting for at least 1 hour. Studies by Klaus et al.[28] indicated that the duration of action was 1 1/2 to 2 hours. Franciosa et al.[29] in 1974 demonstrated that oral short-acting isosorbide dinitrate is well absorbed through the gastrointestinal tract with a physiologic effect lasting up to 4 hours. Nitroglycerin ointment applied to the chest has been shown to have a physiologic effect lasting up to 6 hours.[30]

Beta blocking agents have been used since the early

1970s in treating angina. A double-blind controlled study[31] suggested that the long-term use of beta adrenergic blocking agents improved survival in patients with previous myocardial infarction. It seems reasonable to speculate that the combination of these agents and long-acting nitrates used in appropriate doses to achieve continuous physiologic control of blood pressure and pulse rate has significantly contributed to the improved results with medical therapy in recent years.

Therapeutic implications: The condition of patients with unstable angina pectoris can be stabilized and *acutely* managed with a maximal medical program consisting of the administration of propranolol and long-acting nitrates in pharmacologic doses that achieve therapeutic control of blood pressure and pulse rate. This therapy is successful in most patients. Later, if intensive medical therapy fails, the patient can undergo elective surgery with no increase in risk compared with those patients who undergo early urgent surgery and with excellent results. Patients who are already receiving intensive medical treatment when unstable angina pectoris develops (that is, patients who do not respond to an intensive medical program) should be considered for early bypass surgery if they have suitable coronary arterial anatomic findings on angiography and preserved left ventricular function.

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Logical complement to a diuretic

The effectiveness of Lopressor combined with a diuretic was demonstrated in a study* of 15 hypertensive patients whose blood pressure was reduced on a thiazide alone, and still further reduced when metoprolol was added to the regimen. On a regimen of 100 mg hydrochlorothiazide daily, the maximal response was a mean supine blood pressure reduction of 19/10 mmHg —from a placebo-treatment baseline level of 169/115 mmHg. Following four weeks during which metoprolol 50 mg b.i.d. was added to the regimen, there was a further decrease of 17/13 mmHg.

Mild, transient side effects

Most side effects are mild and transient. The most frequently reported adverse reactions (which

*Mitenko P, McKenzie J: Unpublished study. Data on file, Geigy Pharmaceuticals and available on request.

Usually lacks the side-effect problems of the sympathetic inhibitors

occurred in approximately ten out of 100 patients) are tiredness and dizziness. Depression and diarrhea have occurred in about five out of 100.

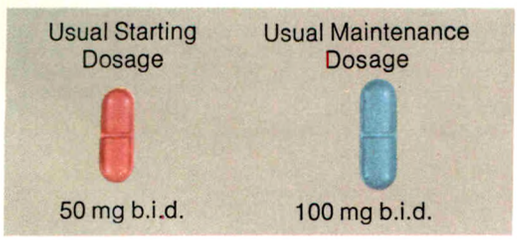
Lopressor usually lacks the side effects of the sympathetic inhibitors which may cause sedation, sexual dysfunction and postural hypotension.

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

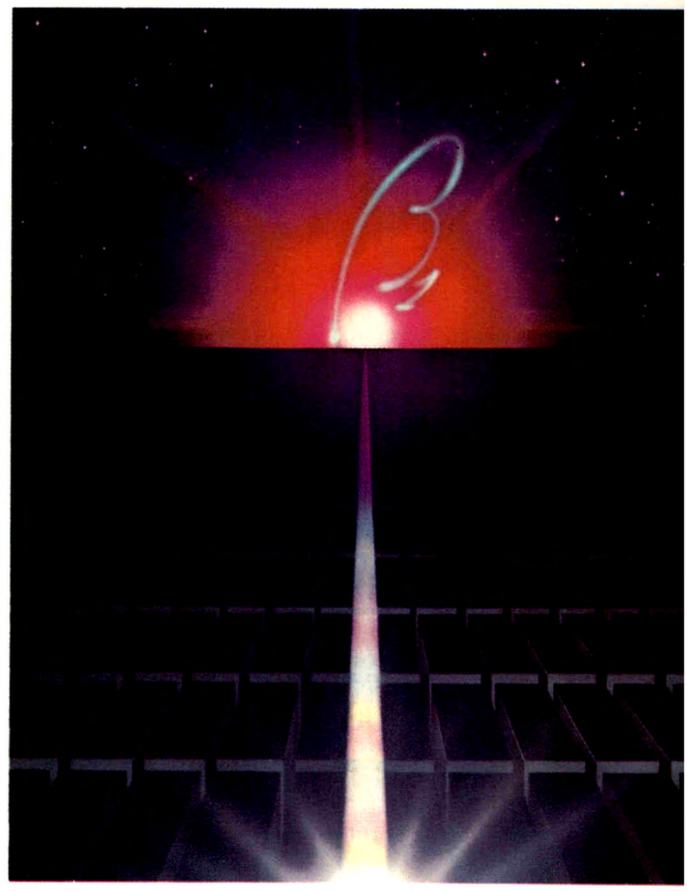
There have been reports of exacerbations of angina pectoris and, in some cases, myocardial infarction following *abrupt* cessation with other beta blockers. Even in the absence of overt angina pectoris, when discontinuing therapy, withdraw Lopressor slowly.

Simple b.i.d. dosage

Patient adherence to the regimen is likely with Lopressor because of its easy-to-remember b.i.d. dosage schedule. The usual starting dosage is one 50-mg tablet twice a day. The usual maintenance dosage is one 100-mg tablet twice a day.



While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. For further details, please see brief summary of prescribing information.



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Contraindications Lopressor, brand of metoprolol tartrate, is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor, brand of metoprolol tartrate, should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor, brand of metoprolol tartrate, therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor, brand of metoprolol tartrate, should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, Lopressor, brand of metoprolol tartrate, may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor, brand of metoprolol tartrate, should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor, brand of metoprolol tartrate, plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor, brand of metoprolol tartrate, should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, Raynaud's disease, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor, brand of metoprolol tartrate, during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor, brand of metoprolol tartrate, should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. $Beta_1$ selectivity diminishes as dosage of Lopressor, brand of metoprolol tartrate, is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

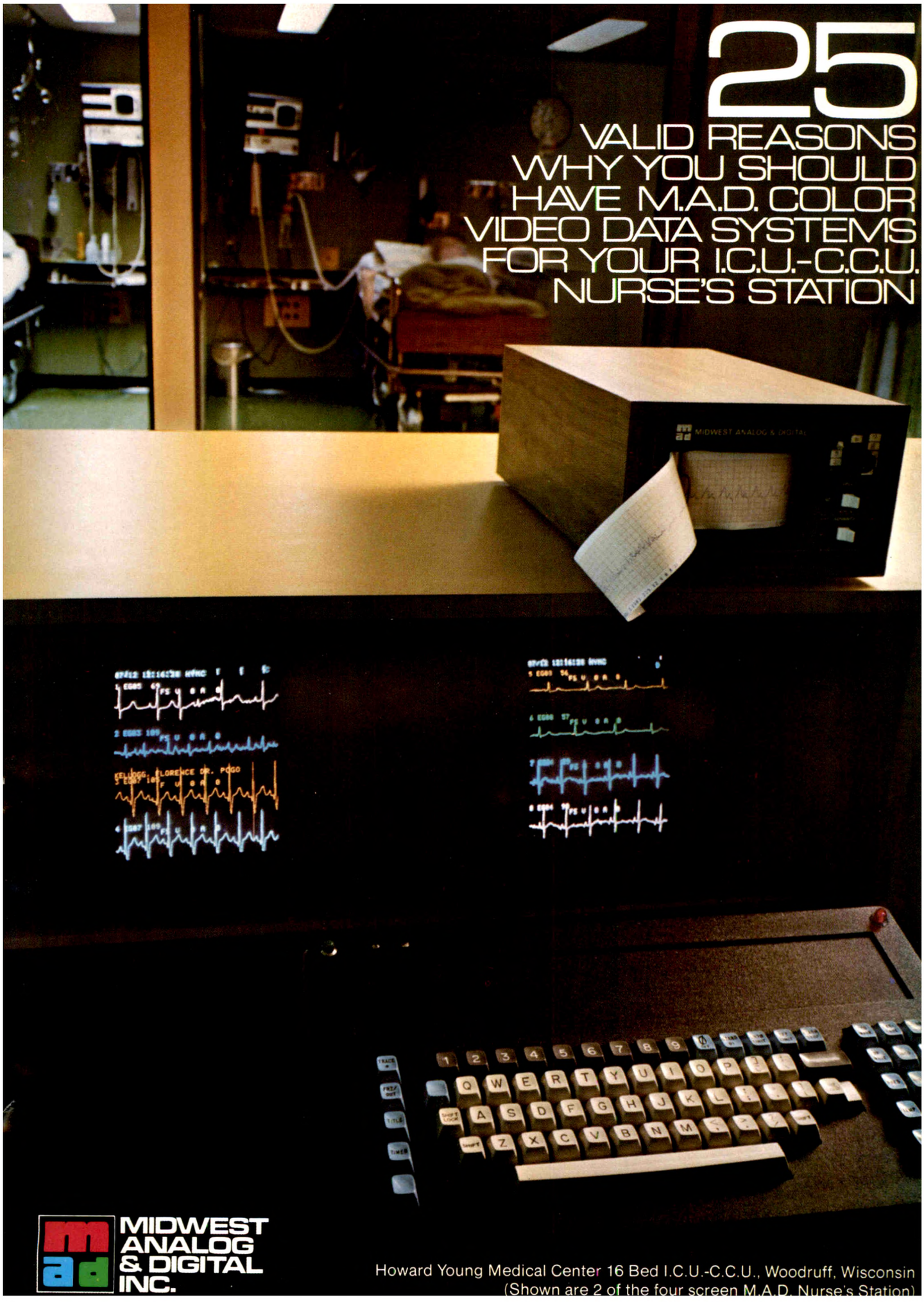
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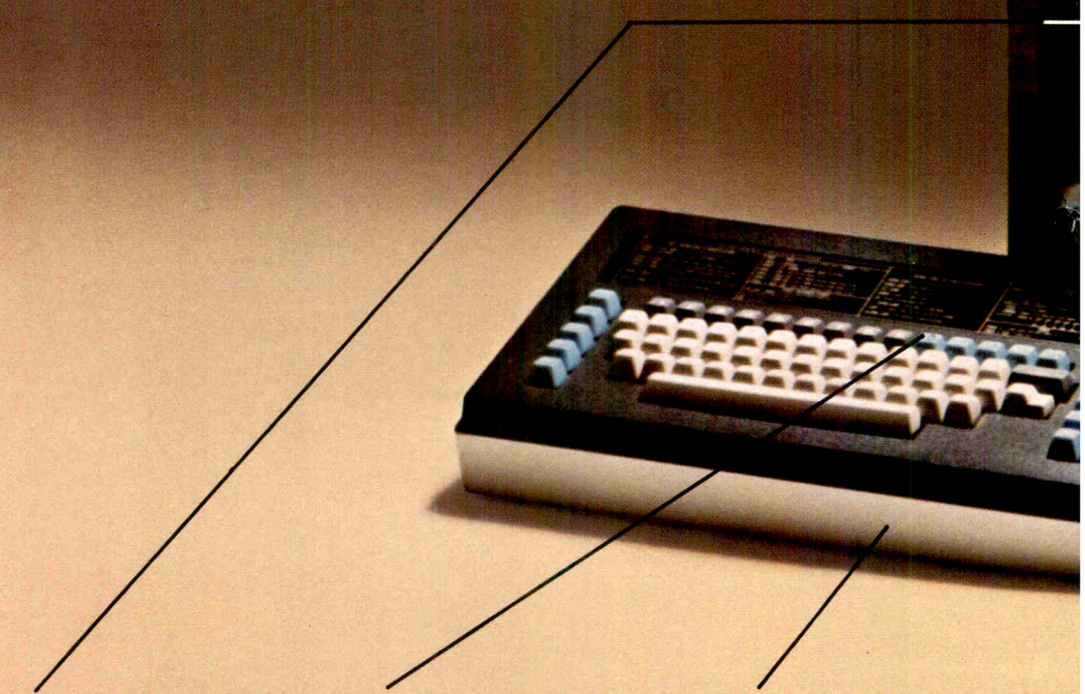
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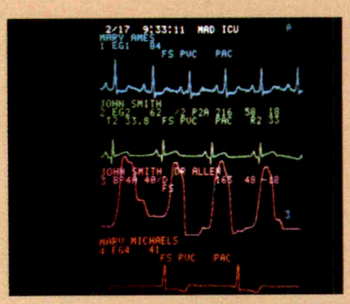
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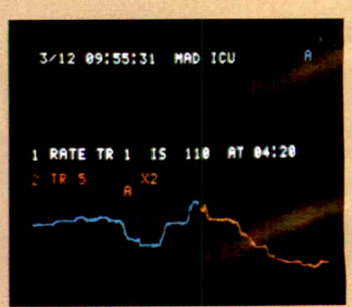
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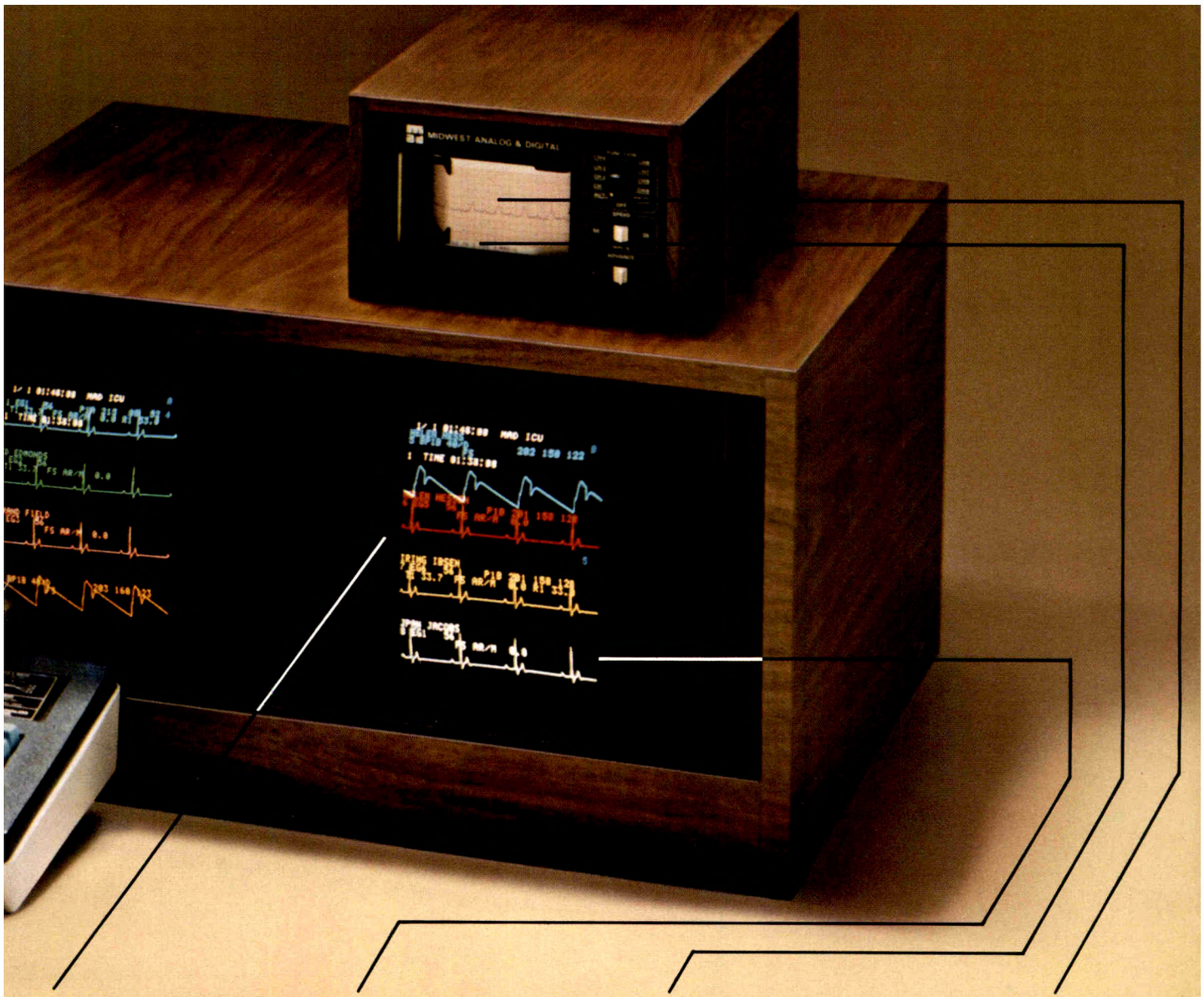
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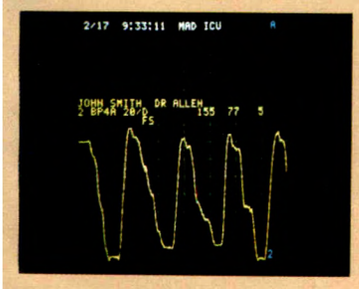


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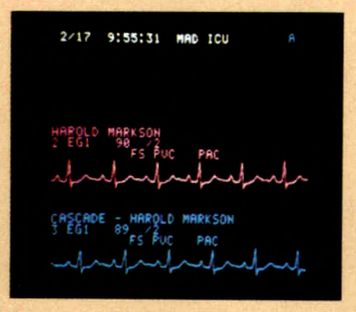
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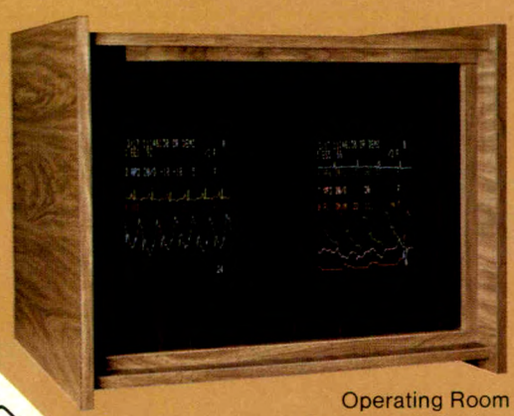
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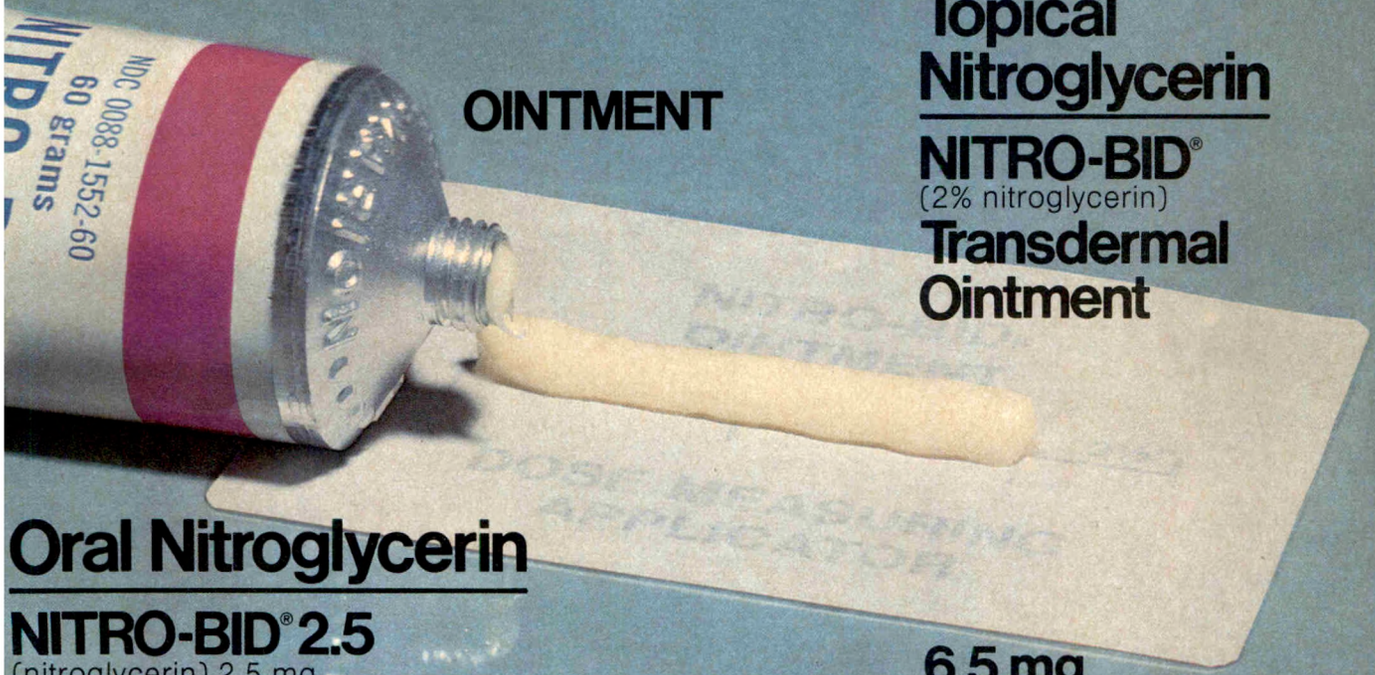
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Based on a review of this drug and a related drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective. When taken by the oral route, NITRO-BID Capsules are indicated for the management, prophylaxis or treatment of anginal attacks.

"Possibly" effective. When applied topically, NITRO-BID Ointment is indicated for the prevention and treatment of angina pectoris attacks especially at night.

Final classification of the less-than-effective indications requires further evaluation.

Contraindications

Patients with marked anemia, increased intraocular pressure, increased intracranial pressure, glaucoma, hypotension, and idiosyncrasy to this drug.

Warnings

NITRO-BID is not intended to abort the acute anginal episode. NITRO-BID Capsules must be taken ORALLY, not sublingually. In terminating NITRO-BID Ointment treatment, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions.

Precautions

A headache is a definite sign of overdosage and, therefore, dosage should be reduced. Occasionally, elderly patients may have no untoward symptoms while recumbent, but may develop postural hypotension with faintness upon suddenly arising.

Adverse Reactions

With use of nitrates, transient headache, postural hypotension, flushing, tachycardia and dizziness may occur.

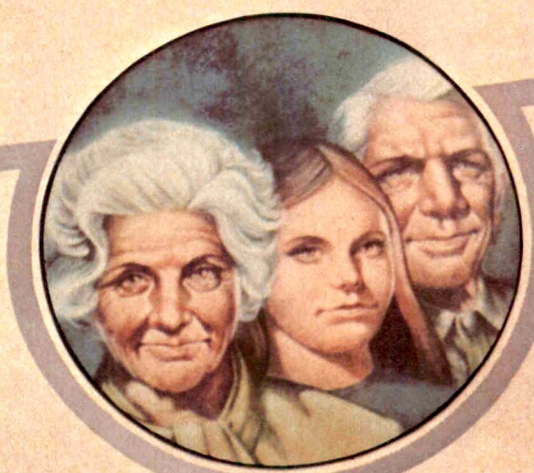
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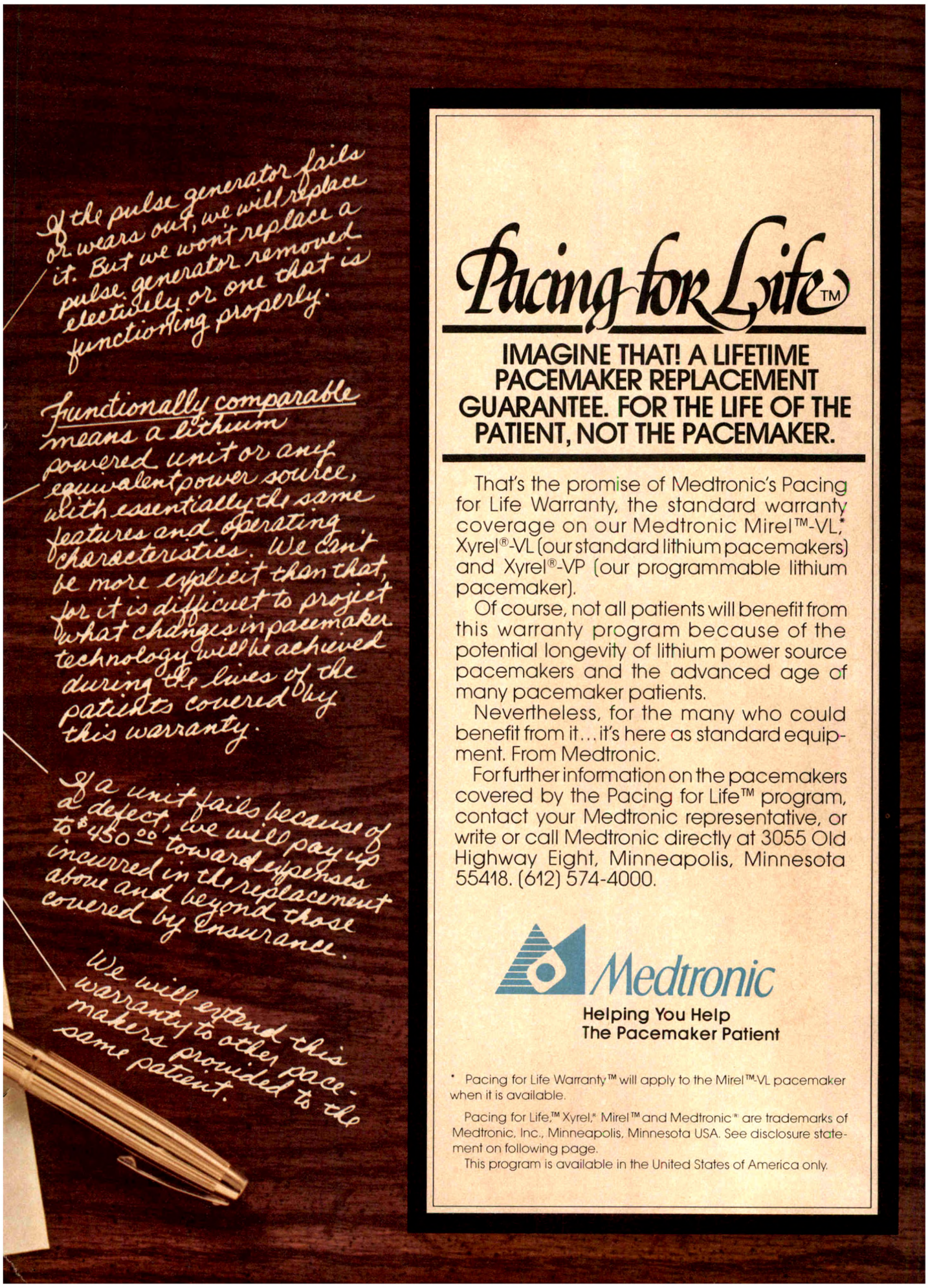
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PRECAUTIONS

The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

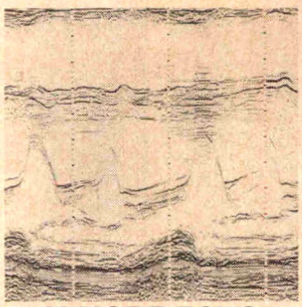
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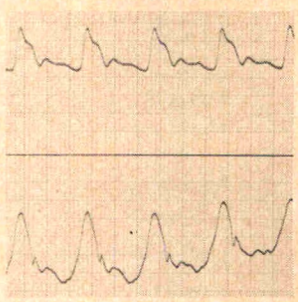
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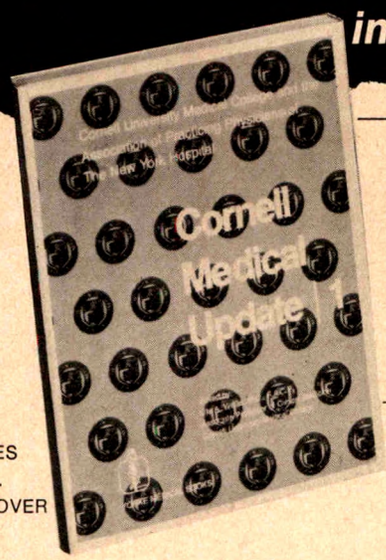
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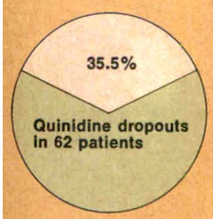
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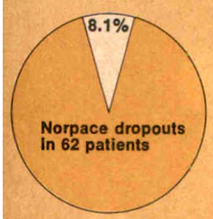
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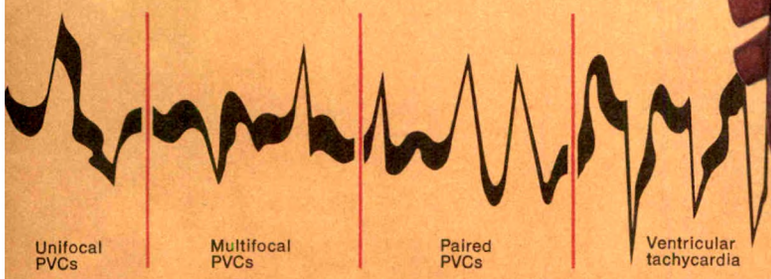
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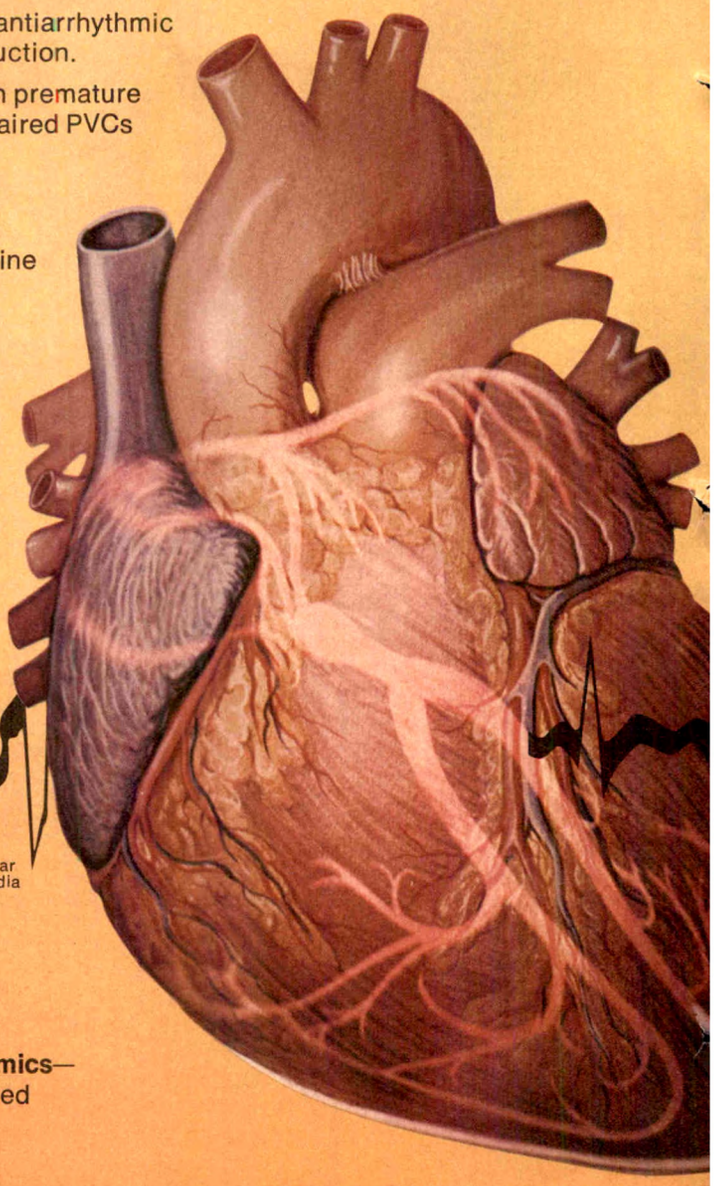
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Dose-related plasma levels—Plasma levels correlate closely with dosage.

Norpace (disopyramide phosphate) effect on hemodynamics—Rarely alters blood pressure significantly at recommended doses. May reduce cardiac output by about 10%.

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:
Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.
Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.
Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished.

In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained with appropriate treatment. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction, evidenced by widening of the QRS complex and/or prolongation of the Q-T interval.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.
Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

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Dosage and administration—Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily.

Initial Norpace dosage

Patients 110 lb or more	150 mg q 6 h
Patients less than 110 lb	100 mg q 6 h
Patients with specific complications: Patients with *possible cardiac decompensation, cardiomyopathy, reduced left ventricular function* or *hypotension* due to these or other causes	100 mg q 6 h
Patients with moderate renal impairment ($C_{Cr} > 40$ ml/min) or hepatic insufficiency	100 mg q 6 h (200-mg loading dose optional)
Patients with severe renal insufficiency ($C_{Cr} < 40$ ml/min)	100 mg given approximately every half-life ($T_{1/2}$) (200-mg loading dose optional)
C_{Cr} = 40–15 ml/min	q 10 h
C_{Cr} = 15– 5 ml/min	q 20 h
C_{Cr} = 5– 1 ml/min	q 30 h
In patients *without the complications* specified above in whom rapid control of arrhythmias is essential, therapy may be initiated with a loading dose of 300 mg (200 mg for patients under 110 lb).	

For complete Norpace dosage recommendations, please see complete prescribing information, a brief summary of which appears below.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy. *Use in Pregnancy and Lactation:* Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, hypoglycemia, (usually in patients with impaired liver function), and dysuria. Acute psychosis and cholestatic jaundice, both reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

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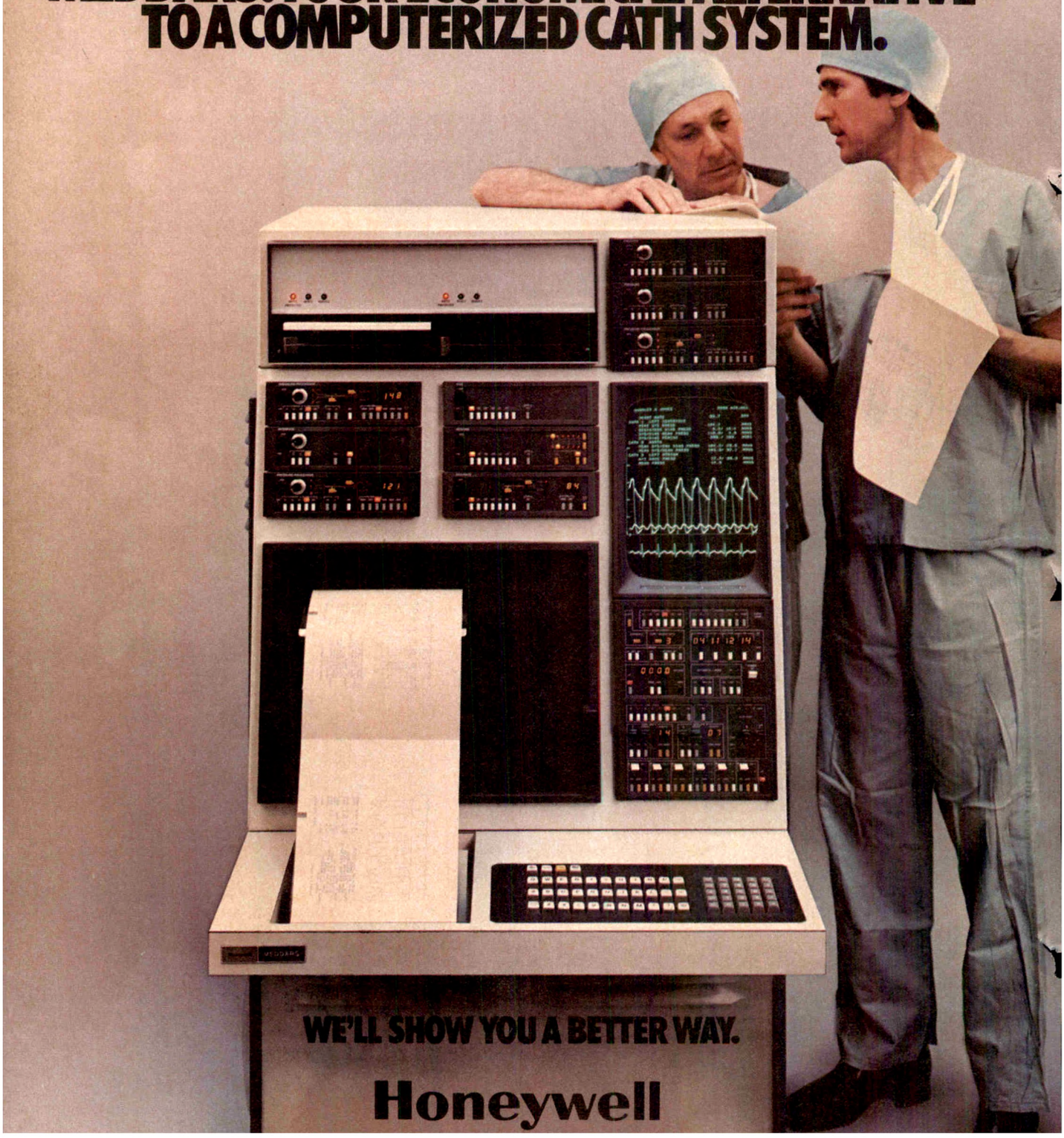
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Centenary of the First Correct Antemortem Diagnosis of Coronary Thrombosis by Adam Hammer (1818–1878): English Translation of the Original Report

J. T. LIE, MD, FACC

Rochester, Minnesota

William Heberden (1710–1801), in 1768, described angina pectoris, the classic symptom of ischemic heart disease, 150 years after the discovery of the coronary circulation by William Harvey (1578–1657). Another 110 years had elapsed before the first antemortem diagnosis (confirmed at autopsy) of coronary thrombosis was reported by Adam Hammer in 1878. The patient was a 34 year old man who died some 19 hours after a sudden collapse. Although the patient's clinical features were atypical (such as the absence of angina and the presence of complete heart block) and the autopsy showed a vegetative aortic endocarditis that appeared to be causally related to the thrombotic coronary occlusion, Hammer's astute and carefully reasoned bedside diagnosis was history-making and deserves to be so recognized.

In 1978, as we commemorate the 400th anniversary of the birth of William Harvey (1578–1657), we are reminded that not only did Harvey describe the systemic and pulmonary circulations, but also he was the first to recognize the *third circulation*—the coronary circulation.[1]

Disease of the coronary circulation is synonymous with coronary atherosclerosis and its consequence, coronary or ischemic heart disease. The classic description of angina pectoris, the leading symptom of ischemic heart disease, was given by William Heberden (1710–1801) before a gathering of the Royal College of Physicians of London on July 21, 1768 and published 4 years later in the College's Transactions.[2] Although Heberden deserves full credit for his observation, he was apparently unaware of the relation between angina pectoris and coronary artery disease. However, before the end of the 18th century, both Edward Jenner (1749–1823) and Caleb Hillier Parry (1755–1822) had correctly related angina pectoris to obliterative disease of the coronary arteries.[3–5]

In 1649 William Harvey mentioned a man who "did often complain of an oppression in the breast . . . at last, opprest in a signal paroxism, he dyed." The autopsy revealed aortic stenosis and rupture of a large left ventricle.[4] The symptoms were typical of angina pectoris, and one must suspect that a myocardial infarct was probably the cause of rupture. This was perhaps one of the earliest recorded cases of autopsy-confirmed angina pectoris, aortic stenosis, acute myocardial infarction with a ruptured ventricle and sudden death. However, Carl Weigert (1845–1904) of Munsterberg, Silesia is universally honored as the first man to record a complete pathologic (autopsy) description of coronary artery disease and myocardial infarction and to identify clearly their cause and effect relation.[6]

Who, then, made the first correct clinical diagnosis of coronary thrombosis with subsequent autopsy confirmation? James B. Herrick (1861–1954) enjoyed this distinction for some time after his classic paper was published in 1912.[7] Although he was preceded by others who had made the correct diagnosis ante mortem (and whom he freely acknowledged in the 1912 paper), Herrick's carefully documented comprehensive

From the Department of Pathology and Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Manuscript received April 3, 1978; revised manuscript received May 23, 1978, accepted May 24, 1978.

Address for reprints: J. T. Lie, MD, Department of Pathology and Anatomy, Mayo Clinic, Rochester, Minnesota 55901.

report attracted the most attention and helped found a secure place for coronary heart disease in clinical cardiology.

The recognition given to the 1910 report by the Russian physicians Obraztsov and Strazhesko is amply justified.[8] (Incidentally, that report did not escape Herrick's attention; he referred to it in his 1912 paper.[7]) Although the undeclared (or unofficial) international dispute over who was first to make an antemortem diagnosis of coronary thrombosis might appear to have been settled by the adjudication of Muller,[8] the name Adam Hammer (1818–1878) should have been mentioned.

One hundred years ago, on January 22, 1878, the first correct diagnosis of coronary thrombosis made during the life of the patient and confirmed later at autopsy was reported in Vienna by Adam Hammer, a Professor of Surgery from St. Louis. Herrick[7] was aware of Hammer's report and referred to it.

The checkered career of Adam Hammer was described briefly by the medical historian Major.[9] Hammer was born in Mingalsheim, Baden. He was graduated as a Doctor of Medicine from the University of Heidelberg in 1842. After the collapse of the revolution of 1848, in which he participated, Hammer fled Germany and sought refuge in America. He arrived in St. Louis in the autumn of 1848 and established a practice. In 1850 he was granted a charter by the Missouri Legislature to establish a medical school, which survived for only 1 year. Nine years later he established another medical school, the "Humboldt Institut," where instruction was given solely in German; this school existed for 10 years. In 1877 Hammer returned to Europe, and in 1878 he started a medical practice in Vienna. He died in the same year, after he had presented his detailed report of a patient with coronary thrombosis.

There were some atypical features in the case described by Hammer, such as the absence of typical anginal chest pain, the presence of a predominant clinical picture of complete heart block and the presence of a vegetative aortic endocarditis that appeared to be causally related to the coronary occlusion found at autopsy. Nevertheless, Hammer's astute and carefully reasoned bedside diagnosis was historically important and deserves recognition.

Hammer's report* was published in the February 2, 1878 issue of *Wiener Medizinsche Wochenschrift.* To date, there has been only an abridged translation of this report in Major's book[9] and another version in an 1878 issue of the *Canadian Journal of Medical Sciences.*[10] I am indebted to my colleague Jurgen Ludwig, MD for the full English translation of Adam Hammer's paper. I accept full responsibility for any errors in the edited translation that follows.

Hammer's Case Report

All pathologic changes that occur in the arterial system, such as endarteritis, atheromatosis, aneurysm, stenosis, calcification, ossification and thromboembolism with their complications, including infarct, abscess and other focal disturbances, can often be found in the coronary arteries at autopsy. In living patients, however, thrombosis of one or both coronary arteries has not yet been recognized. When I first made this diagnosis, I considered the situation a new one because I had never heard about it before, nor had I read about it. I could have published my observation then, without any hesitation, but at the time did not quite feel like writing, and I was still uncertain that there might have been a published report about this which had escaped my attention. The great interest that the case has aroused in me caused me to bring up the matter, during a visit to New York in the spring of 1877, with the chairman of the Medical Society. Even the learned Doctor Jacoby, whom one could call a living medical dictionary, knew nothing about this condition. Since arriving back in this continent, I have also asked many clinicians when traveling across the country, among them Kussmaul in Strassburg and Bamberger in Wien. None could give me any information. All declared that they had never seen such a case, nor had they ever read about it. This, and the fact that many of the aforementioned gentlemen urged me not to keep this case from the public any longer, prompts me to make the following report.

On May 4, 1876, at 9:00 A.M., a young friend and colleague of mine, Dr. Wichmann, took me to see a sick person whose condition had puzzled my friend. He related to me the following story.

The patient, Jakob Schreier, was a 34 year old married merchant with an athletic build who was a heavy beer drinker and who for some years had had repeated attacks of rheumatoid arthritis. Changes in the valves of the heart had never been diagnosed. Four weeks ago, the patient had again had a very acute attack in several joints. He slowly recovered and felt rather well for a short time. His pulse rate was 80 beats/min. Yesterday, May 3, he got out of bed shortly before noon and sat down in his chair. At 1:00 A.M. the patient suddenly collapsed in his chair. Dr. Wichmann saw him 30 minutes later and found that he had a weak pulse of only 40 beats/min with pale lips, and was somewhat cyanotic and mildly dyspneic but experienced no pain. In the beginning, Dr. Wichmann thought the collapse was due to a massive effusion in the pericardial cavity, but he was uncertain. At 6:00 P.M., the patient's pulse was weaker, only 23 beats/min, and at 10:00 P.M. the pulse rate was 16 beats/min; everything else remained the same.

I found the patient in the following condition. He was straightened out in his bed, slightly elevated on his back, with the hands quietly placed on the blanket. The pulse rate, 8 beats/min, was half as slow as the evening before at 10 P.M. His face and skin were pale, cool and covered with sticky sweat. His eyes were clear and the pupils were of medium size and reacting; he had mild cyanosis around the lips and tongue and mucosa of mouth, and his forehead was pale and anemic. He had no dyspnea, no cough, no expectoration and no pain. His respiration rate was 24 breaths/min. The senses were not impaired. The patient faced the situation as if he did not recognize how sick he was.

On physical examination, the percussion of the heart gave no abnormal result. The heart could be palpated easily and was normal in position and size. The percussion of the lung also appeared normal in that there was no evidence of pneumonia or pleural effusion. Auscultation of the lung revealed normal respiratory sounds with only a few fine rales such as those that occur in marked hyperemia of the lung.

Auscultation of the heart revealed a peculiar finding. The heartbeat was weak, one beat every 8 seconds regularly. After the systolic and diastolic heart sounds, which were weak but

* A case of thrombotic occlusion of a coronary artery of the heart: Diagnosed clinically and reported by Dr. A. Hammer, Professor of Surgery from St. Louis, currently in Vienna. Wien med Wchnschr 28: 97–102, 1878

clearly audible and without bruits, there followed a clonic spasm of the heart that hit the ear with a strong vibration, lasting about 5 seconds with the same intensity, and then stopped suddenly. I could not compare these rapid contractions of the myocardium better than to a rapid trembling of the hand of a human being that has delirium tremors. After this, there was silence for 2 seconds and then again a normal heart contraction of 1 second, spasm of the heart for 5 seconds, absolute quiet for 2 seconds, and so on. For 20 minutes I continued the auscultation and never did I recognize any change in this process. A systolic or diastolic bruit could not be recognized.

Study of the abdominal viscera and the head and neck area revealed no abnormalities. This completed the physical examination. We did not know what to do with these peculiar findings and were all perplexed about it. I tried to make a diagnosis by exclusion.

The symptoms did not fit fatty change of the heart or a dilated heart. The findings of the physical examination and other aspects of the case contradicted these diagnoses. In addition, the symptoms of both diseases are so variable that the opinions of most authors differ very much in how to make the diagnosis, and some even doubt that the differentiation can be made at all.

There was no reason to suspect that disturbances of innervation played a role. The patient had normal senses, and so there was no evidence of a central nervous system abnormality that could have affected the nerves. The peripheral nerves, particularly in the neck area, showed no abnormality.

Infectious diseases were excluded because the symptoms were absent. Abnormal pressure was unlikely because there was nothing to indicate it, based on the percussion of the heart and auscultation. Other diseases such as myocarditis, endocarditis, hypertrophy, atrophy and valve changes were also excluded because of the negative findings on auscultation and percussion and because other symptoms for such disease were lacking.

What was left? Nothing, absolutely nothing, that would not have been known already. In this desperate situation, I wondered if a disturbance of the nourishment of the heart could explain such a condition, and whether this could have been caused by thrombotic occlusion of at least one coronary artery. I had no other sufficient explanation and had this thought intuitively. Further consideration indicated that only one coronary artery could have been occluded. This was suggested by the slow deterioration of the collapse. If both arteries had been thrombosed, the activity of the heart would have decreased much more quickly or would have come to a complete standstill. Even more supportive of this idea of only one vessel being affected was the observation of the heart spasm that recurred every 5 seconds. If one considers that one half of the heart needs about 8 seconds of rest to contract again while the other half functions normally, then it is comprehensible that the healthy half, being connected with the diseased one, cannot produce rhythmic movements. The diseased half must be looked upon as a transiently dead mass that is shaken by the second half. These thoughts supported my conviction that we were dealing with a thrombosis of only one coronary artery. Whether it was the right or the left one was impossible to speculate. I expressed my conviction to my colleague while we were at the bedside. He looked very perplexed and exclaimed, "I have never heard of such a diagnosis in all my life." Whereupon I answered, "Nor have I." He couldn't calm down and seemed to think that I had hidden my confusion behind a bad joke. I tried to convince him that I was serious by giving him all the reasons for this diagnosis, and I assured him that I not only believed in it but was firmly convinced of it. Both of us had the same great interest in the case, and I had no greater desire than to determine the correctness or incorrectness of my diagnosis.

Since the patient had only a few more hours to live, we could confirm the diagnosis by conducting an autopsy. For that reason, Dr. Wichmann would try hard to get permission for an autopsy from the relatives. (Even in America today it is still very difficult to do an autopsy. Very often I have had to obtain permission by offering an honorarium. Yes, in some cases I had to put money on the table in order to secure the permission. This universal remedy seems to efface even the most profound hesitation, including one on religious grounds.)

Surprisingly, the patient lived another 19 hours. He died on the morning of May 5. Wichmann obtained permission for a limited autopsy. We were only permitted to take the heart out; no other organs were to be touched. For our purpose this was enough, and we were content to have gotten that far. On May 6 at 11:00 A.M., 29 hours after the death, we proceeded with the partial autopsy while the body was already dressed up in a coffin.

Autopsy: After the sternum had been lifted up so that the heart was clearly visible and could be taken out, one could see the anterior edges of both lungs under the ribs covering most of the mediastinum. The lungs were enlarged, dense and dark, undoubtedly because of hyperemia and edema. The outer surface of the pericardium showed nothing abnormal. In the pericardial cavity, there was one half ounce of clear yellow serum. The walls were smooth and shiny. The heart was in its proper position, of normal size and shape and appeared quite tense. The surface was smooth and shiny, and there was abundant fat around the coronary arteries. Otherwise, there were no abnormalities.

After the heart had been taken out, the cavities were studied. The right atrium and ventricle were filled with thick coagulated blood, abundant fibrin and lobular vegetation (developed in the agonal period or post mortem). The cavities of the atrium and the ventricle were of normal size. The tricuspid and semilunar valves of the pulmonary artery were intact. The color of the myocardium on cut section was pale with a brown-yellow tinge. The wall of the ventricle was of normal thickness. The endocardium was unchanged.

Everything said about the right atrium and ventricle and their valves also held true for the left atrium, ventricle and valves, except for the semilunar valves of the aorta, where we found peculiar changes that we had already noticed when examining the aortic valve from above. In order to study this in more detail, I split the aorta and thus exposed the commissure of the right and left cusps; this maneuver turned out to be very useful. If I had placed the cut through the commissure of the posterior and right valve as was usually done, an important part of our findings would have been destroyed and the exact insight into the origin and development of the abnormal process would have been lost. The first thing that fell into our view was the complete tension and outpouching of the right cusp by a mass that not only filled the right sinus of Valsalva but extended above it in a lobular fashion. After careful removal and study of this mass, we discovered that the uppermost layers consisted of a soft white and yellow bloody fibrin that reached all the way into the takeoff of the (right) coronary artery. From the (right) coronary artery ostium downstream, the nature of this fibrinous mass changed. It became increasingly paler and drier and showed a grey-red color. All of these properties of a thrombus were most pronounced in the lowermost layer, and inseparably attached to it a thin filament took off that was about 2 1/2 cm in length and adherent to the clot.

The aortic valves were not thickened but smooth and shiny, and the posterior cusp was fused with the left and the right cusps at the commissures over a short length of 4 mm. Accordingly, there were fresh soft whitish endocarditic excrescences underneath these (fused commissures), which were not very extensive and affected the ostium of the aorta in only a limited way. These excrescences looked like little pillows that formed a fine network of granulation tissue resembling a condyloma, hanging free into the lumen of the artery.

This autopsy confirmed the diagnosis convincingly. There is no doubt that during the first formation of the thrombus in the right sinus of Valsalva, the patient felt relatively well until the thrombus reached the takeoff point of the coronary artery; at this point the collapse occurred and the continued decrease in pulse rate was caused by the continued increase of the thrombus up to the point of complete occlusion. The autopsy also explained the origin of the thrombus and how it formed. No doubt there were mechanical causes. The wart-like excrescences hanging free in lumen of the aorta were the mechanical trigger. On the tip of these formations, the first fibrin clot precipitated. When the first thrombus became heavier and heavier by increased fibrin deposition that could no longer be carried by the excrescences, the thrombus settled by its own weight into the right sinus of Valsalva and pulled the excrescences down with it. The fine filament already mentioned was probably the elongated tip of these excrescences and for that reason could not be separated from them without force. Had I cut into the aorta through the commissure between the posterior and right cusps, the warty excrescences with their fine papillae might have been dislodged, and we would not have been able to trace the origin of the thrombus.

This case revealed many other interesting aspects that should be studied and discussed. However, the length of this article has transgressed the limits of normal journal articles, and we should wait for a better time for the discussion after more cases of this type have been observed, which is bound to happen if clinicians turn their attention to it. We would also expect the experimental pathologist to study this matter in the near future.

The intelligent and brilliant Cohnheim would be interested in this case. When he made the following remarks in his lecture on general pathology published in 1877, little did he know that the answer would be forthcoming within 18 months. He remarked: "Indeed Bezold has occluded the coronary artery with clamps and by artificial embolization and in this way has brought the heart to a standstill. It seems unlikely to me that a similar event could ever be observed in human pathology."

The specimen I have described is in the hands of my friend, Dr. Wichmann.

Vienna, January 22, 1878.

Comments on Hammer's Case

This was no ordinary case report, but a complete clinicopathologic conference of the highest caliber, with Hammer the "solo performer" playing multiple and all roles.

The scenario began with Act 1: Hammer, the "moderator," cautiously pointed out that the case to be discussed was a hitherto unknown or unrecognized clinical entity. In Act 2, Hammer the "resident physician" presented the protocol with all pertinent history and the results of the physical examination. In Act 3, Hammer, the "visiting professor," succinctly discussed the clinical problem and offered and quickly dismissed the various improbable differential diagnoses. He then, without the help (or perhaps the hindrance) of electrocardiographic and serum enzyme data, dropped a bombshell by proposing that the patient had coronary thrombosis, a diagnosis that had never been made before. In Act 4, with the audience still in suspense, Hammer, the "pathologist," described the autopsy findings in minute detail, verifying the visiting professor's astute analysis and bold prediction. Since the audience was too dumbfounded to ask questions, Hammer the "moderator" proceeded to adjourn the meeting by suggesting that ". . . we should wait for a better time for the discussion after more cases of this type have been observed, which is bound to happen if clinicians turn their attention to it." He further predicted: "We would also expect the experimental pathologist to study this matter in the near future."

Unquestionably, it was a memorable performance.

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DIAGNOSTIC SHELF

Cross-Sectional Echocardiographic Diagnosis of Large Left Atrial Tumor and Extracardiac Tumor Compressing the Left Atrium

Limitation of M Mode Echocardiography in Distinguishing the Two Lesions

JUNICHI YOSHIKAWA, MD
IRFAN SABAH, MD
KOJI YANAGIHARA, MD
TAKANE OWAKI, MD
HIROSHI KATO, MD
KIICHIRO TANEMOTO, MD

Kobe, Japan

A case of a left atrial fibrosarcoma arising from the posterior left atrial wall and two cases of an extracardiac tumor compressing the left atrium were studied with M mode and cross-sectional echocardiography. In all three cases, M mode echocardiography revealed a mass of echoes just behind the aorta and did not distinguish a left atrial from an extracardiac tumor. By contrast, cross-sectional echocardiography allowed direct visualization of the location, size and movement of the tumor in all three cases and contributed to distinguishing the two lesions. This study indicates that cross-sectional echocardiography is more accurate than M mode echocardiography in the differential diagnosis of a large left atrial tumor and extracardiac tumor compressing the left atrium.

The value of M mode echocardiography in the diagnosis of a left atrial myxoma has been well documented.[1–5] The diagnosis is suspected from the presence of a group of echoes posterior to the anterior mitral valve. This group of echoes may almost completely fill the left atrium during both systole and diastole when the tumor is extremely large.[6] Recently, we observed three patients whose M mode echocardiograms suggested the presence of a large left atrial myxoma. However, cross-sectional echocardiograms revealed that one had an intraatrial mass arising from the posterior wall of the left atrium, and the remaining two had an extracardiac tumor compressing the left atrium. Thus in this paper we report (1) the occurrence of an M mode echocardiographic pattern mimicking a left atrial tumor in patients with an extracardiac tumor, and (2) the ability of cross-sectional echocardiography to distinguish left intraatrial from extracardiac tumors.

Ultrasonic Techniques

Cardiac echograms were performed with an Aloka SSD-110 echograph using a 2.25 megahertz transducer, 13 mm in diameter and collimated to 7.5 cm. Records of sector M mode scans were made with a Fukuda Denshi ECO-125 or an Aloka SSZ-71 strip chart recorder.

Cross-sectional echocardiograms in Case 1 were obtained with a contact sector scanner gated to an electrocardiogram (Aloka SSD-90), using a 2.25 megahertz transducer. The plane of the scanning arm was adjusted to correspond with the long axis of the heart. A gating circuit triggered by the patient's electrocardiogram was used to activate the recording storage oscilloscope for a preselected brief interval during successive cardiac cycles. A permanent record was made on 35 mm film from the oscilloscope. In Cases 2 and 3, cross-sectional examination was performed using a real-time imaging system (Aloka SSD-111). A 2.25 megahertz transducer mechanically driven through an approximately 60° sector at a variable rate from 5 to 40 frames/sec was utilized. Images were permanently recorded on 8 mm cinefilm and videotape; phase-selected single frames were recorded on Polaroid® film using the electrocardiographic circuit.

From the Department of Cardiology, Kobe Municipal Central Hospital and Department of Medicine, Kobe Rosai Hospital, Kobe, Japan. Manuscript received March 28, 1978; revised manuscript received June 6, 1978, accepted June 7, 1978.

Address for reprints: Junichi Yoshikawa, MD, Department of Cardiology, Kobe Municipal Central Hospital, Kano-cho 1-5, Ikuta-ku, Kobe, Japan 650.

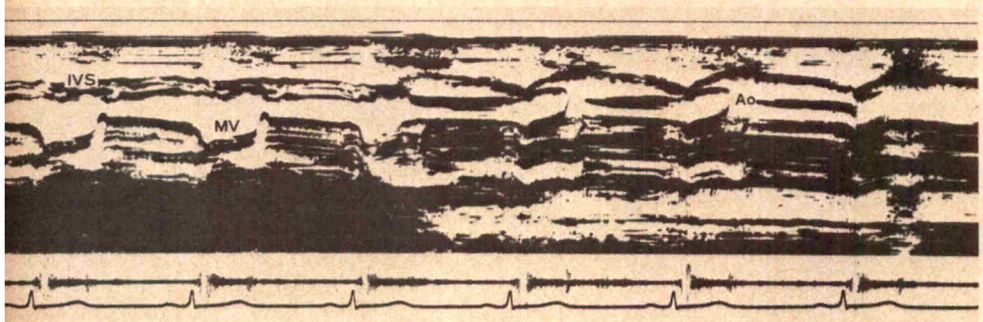


FIGURE 1. Case 1. M mode echocardiogram. Scan from the mitral valve (MV) to the aorta (Ao) reveals a mass of dense layered echoes posterior to the anterior mitral valve and the aorta. IVS = interventricular septum.

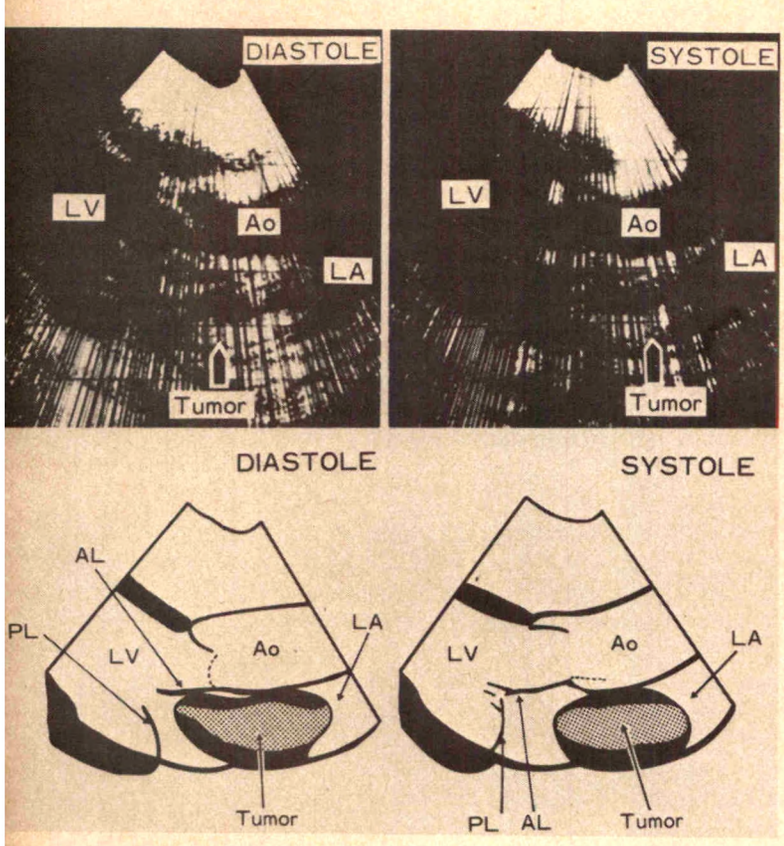


FIGURE 2. Case 1. Cross-sectional echograms through the long axis of the aorta (Ao) (**upper panel**) and their schematic illustrations (**lower panel**). A large mass of echoes arising from the posterior wall of the left atrium (LA) moves toward the mitral orifice in diastole and cephalad in systole, although the range of motion is very limited. AL = anterior mitral leaflet; LV = left ventricle; PL = posterior mitral leaflet.

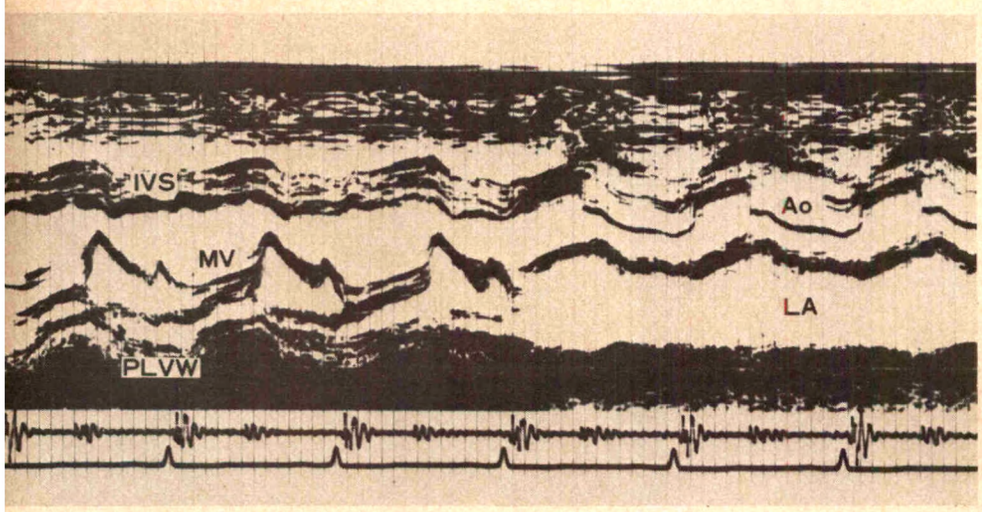


FIGURE 3. Case 1. Postoperative M mode echocardiogram. No abnormal echoes are seen in the left atrium (LA) or in the region of the mitral valve (MV). Ao = aorta; IVS = interventricular septum; PLVW posterior left ventricular wall.

Case Reports

Case 1: A 43 year old man was found to have a heart murmur during an examination for abdominal pain and was referred to us for cardiac evaluation. Physical examination revealed a grade 3/6 systolic murmur, a grade 2/6 mid diastolic rumbling murmur and an early diastolic sound over the apex. The first heart sound was loud, but not split. The second sound was normally split and its pulmonary component was accentuated. A chest roentgenogram revealed moderate cardiac enlargement and mild pulmonary congestion. An electrocardiogram was normal.

An M mode echocardiogram (*Fig. 1*) revealed a group of dense layered echoes posterior to the anterior mitral valve. This group of abnormal echoes occupied the latter three fourths of diastole. As the transducer was rotated from the mitral valve region toward the aorta, the dense layer of abnormal echoes almost completely filled the left atrium. The space between the aorta and these densely layered echoes was extremely narrow.

Cross-sectional echocardiograms (*Fig. 2*) revealed a large mass of echoes arising from the posterior wall of the left atrium. This mass of echoes moved toward the mitral orifice in diastole and cephalad in systole, although the range of motion was very limited. No abnormal echoes were observed behind the left atrium. The diagnosis of a mobile tumor arising from the posterior wall of the left atrium was made on the basis of these ultrasonic features. Cardiac catheterization was not performed.

The patient underwent open heart surgery. When the left atrium was entered, a large tumor (72 g) was found originating from the posterior wall of the left atrium. The tumor almost completely filled the chamber. The intracavitary portion of the tumor was excised completely. Histologically, the tumor was interpreted as a fibrosarcoma.

The postoperative M mode and cross-sectional echocardiograms (*Fig. 3 and 4*) revealed complete absence of the abnormal echoes previously found posterior to the anterior mitral valve and the aorta. However, about 1 month after operation, the patient died with multiple metastases.

Case 2: A 59 year old man was admitted to the Kobe Municipal Central Hospital because of proved esophageal carcinoma. He was referred for cardiac evaluation because of electrocardiographic abnormalities detected during a routine examination. He was emaciated and dehydrated. A grade 2/6 systolic ejection murmur was audible over the apex of the heart. During diastole no murmur or extra sound was audible. A chest roentgenogram revealed moderate cardiac enlargement and normal pulmonary vascularity. Serial electrocardiograms revealed increasing S-T segment depression in the left precordial leads and paroxysmal atrial fibrillation.

An M mode echocardiogram (*Fig. 5*) revealed a cloud of abnormal echoes posterior to the aorta but no abnormal echoes behind the mitral valve. The position of the posterior wall of the left atrium could not be determined. Therefore, a tentative diagnosis of a metastatic tumor in the left atrium or an abnormal mass in the vicinity of the left atrium was made.

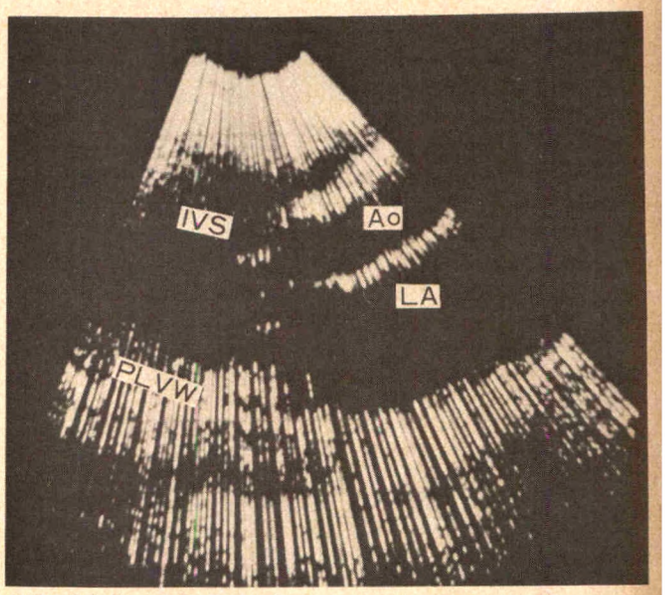


FIGURE 4. Case 1. Postoperative cross-sectional echogram through the long axis of the aorta (Ao). The mass of echoes is no longer present. IVS = interventricular septum; LA = left atrium; PLVW = posterior left ventricular wall.

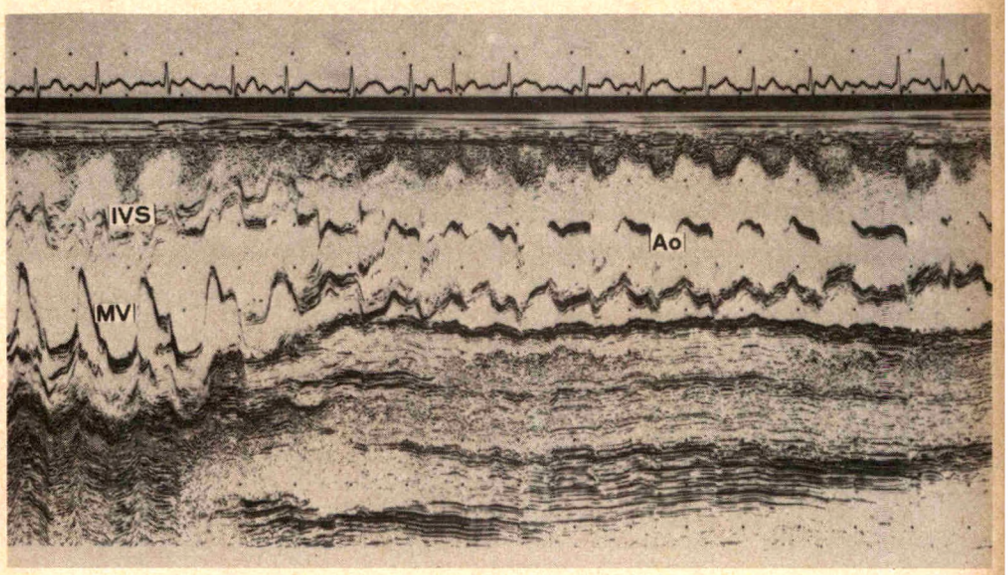
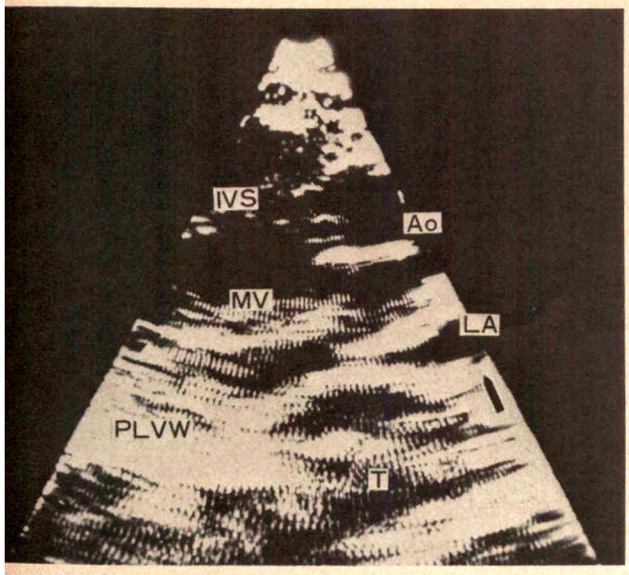


FIGURE 5. Case 2. M mode echocardiogram. A cloud of echoes is seen just behind the aorta (Ao). A tentative diagnosis of a metastatic tumor in the left atrium or an abnormal mass in the vicinity of the left atrium can be made. IVS = interventricular septum; MV = mitral valve.



IGURE 6. Case 2. Cross-sectional echogram through the long axis of ıe aorta (Ao). There is a huge mass in the vicinity of the left atrium (LA). he leading edge of the tumor (T) has a curved shape. In addition, the pper posterior left atrial wall (**arrow**) is visualized and it has a normally urved or straight configuration. This line of the posterior wall is inter- ıpted by the convexity of the tumor. IVS = interventricular septum; IV = mitral valve; PLVW = posterior left ventricular wall.

A real-time cross-sectional echocardiogram (*Fig. 6*) dis- losed a huge immobile mass in the vicinity of the left atrium. 'he leading edge of the tumor had a curved shape. The tumor vas judged to be of extracardiac origin on the basis of the ollowing observations: (1) The upper posterior left atrial wall ould be visualized and it had a normally curved or straight onfiguration; (2) this line of the posterior wall was inter- upted by the convexity of the tumor; and (3) the tumor was mmobile. The tumor was assumed to have arisen from the sophageal carcinoma. On the 42nd hospital day, the patient's ondition suddenly deteriorated and he died in a state of low ardiac output.

Autopsy revealed in the middle lower portion of the sophagus a huge tumor that compressed the left atrium and left main pulmonary vessels. No left intraatrial mass was observed, but the tumor was seen to invade the left bronchial tree.

Case 3: A 71 year old man was admitted to our hospital because of vague chest pain. No significant murmur was audible. The first heart sound was normal and the second sound was normally split. A prominent left ventricular impulse was present. A chest roentgenogram revealed moderate cardiac enlargement and mild pulmonary congestion. An electrocardiogram was normal. An upper gastrointestinal X-ray series revealed moderate anterior displacement of the middle lower portion of the esophagus.

An M mode echocardiogram (*Fig. 7*) revealed a cloud of echoes posterior to the mitral valve and the aorta. These abnormal echoes behind the mitral valve were observed throughout the cardiac cycle. The space between the aorta and the abnormal echoes was extremely narrow.

Cross-sectional echocardiograms (*Fig. 8*) demonstrated behind the heart a giant mass of echoes that compressed the left atrium and moved only slightly. A diagnosis of mediastinal tumor was made.

An angiocardiogram obtained from a pulmonary artery injection showed a large filling defect in the region of the mitral ring and the left pulmonary artery. No filling defect was seen in the right ventricle or atrium. Cardiac catheterization revealed a mild increase (15 mm Hg) of pulmonary arterial wedge pressure.

Thoracotomy on the 15th hospital day revealed a large tumor located in the posterior mediastinum. The relation between the tumor and the lung was not disclosed. Histologically, the tumor was interpreted as a small cell carcinoma. It was judged nonresectable. The patient was therefore treated with anticancer drugs and radiotherapy.

Discussion

M mode echocardiography has been used extensively in the diagnosis of left atrial myxoma.[1–5] Cross-sectional echocardiography has been shown to be of value in complementing M mode echocardiography by enhancing the delineation of anatomic and spatial orientation of the lesion.[7] Our study demonstrates the contribution of ultrasound to the diagnosis of other tumors including a left atrial fibrosarcoma and extracardiac tumors located in the posterior mediastinum.

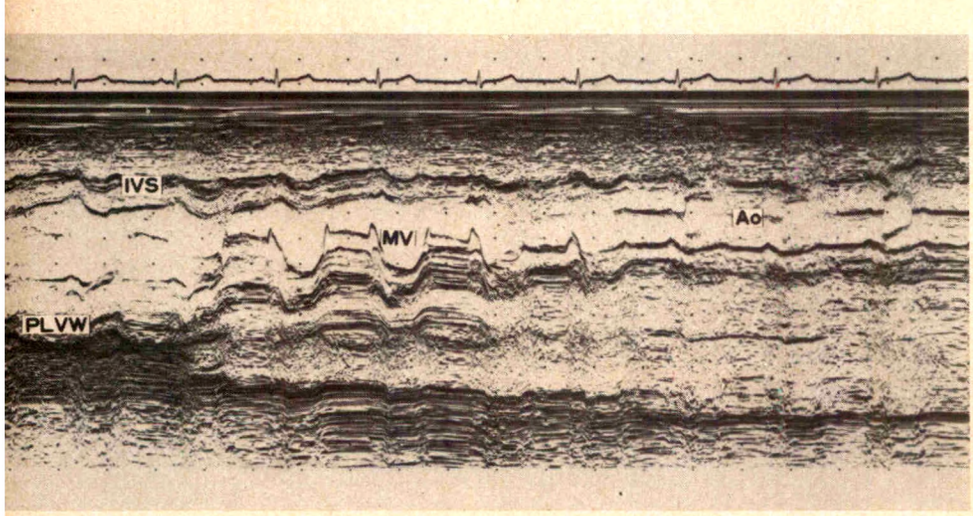


FIGURE 7. Case 3. M mode echocardiogram. A cloud of echoes seen behind the mitral valve (MV) and the aorta (Ao) simulates a large left atrial tumor. IVS = interventricular septum; PLVW = posterior left ventricular wall.

The M mode echocardiographic features of a left atrial fibrosarcoma, documented in this study, included (1) a group of dense layered echoes, and (2) almost complete filling of the left atrium by such echoes. These features resemble the previously described pattern of a left atrial myxoma of huge size.[6] A similar M mode echocardiographic pattern was also observed in two patients with an extracardiac tumor compressing the left atrium. In these patients, a mass of echoes originating from the extracardiac tumor was seen just behind the aorta and mimicked a large left atrial tumor. Therefore, it is hazardous to interpret such an echocardiogram too specifically. When a cloud of echoes behind the aorta is observed, two diagnostic possibilities should be considered: a large left atrial tumor or an extracardiac tumor compressing the left atrium. These two entities may be difficult to distinguish, but the echographic pattern behind the anterior mitral valve may be helpful. The area behind the mitral valve is relatively free of echoes during systole and the initial part of diastole in patients with a left atrial tumor, whereas this characteristic pattern does not occur in the presence of an extracardiac tumor (Case 2). Nevertheless, an extracardiac mass may produce abnormal echoes behind the mitral valve that can be confusing with M mode echocardiography, as in Case 3.

Cross-sectional echocardiography, by contrast, allowed direct visualization of the location, size and movement of the tumor in all three cases. In addition, it permitted recording of the posterior wall of the left atrium, which contributed to distinguishing a left atrial from an extracardiac tumor. In the patient (Case 1) with a left atrial fibrosarcoma, a mass of echoes was seen arising from the posterior wall of the left atrium and extending into the left atrial cavity; it moved toward the mitral orifice in diastole and cephalad in systole. The tumor echoes that almost completely filled the left atrium preoperatively were no longer present in the postoperative cross-sectional echocardiograms. In the patients (Cases 2 and 3) with an extracardiac tumor, a large mass of echoes was noted behind the heart with little movement throughout the cardiac cycle. In addition, the compression of the left atrium by the mass of echoes was clearly demonstrated. Cross-sectional echocardiography thus proved to be a useful tool in visualizing the size and motion of each tumor and in distinguishing a left atrial from an extracardiac tumor.

This study demonstrates the potential ability of cross-sectional echocardiography to visualize neoplasms located in the posterior mediastinum. Because this technique visualizes only a small area of the mediastinum it may prove applicable in only a limited number of patients. However, it may be of value in detecting tumors that mimic mitral stenosis or left atrial myxoma.

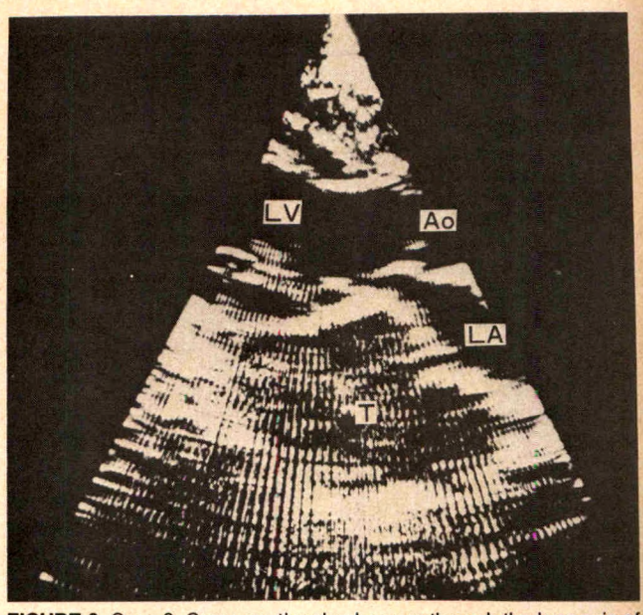


FIGURE 8. Case 3. Cross-sectional echogram through the long axis of the aorta (Ao). A huge mass of echoes (T) is located behind the heart and compresses the left atrium (LA). LV = left ventricle.

Cross-sectional echocardiography has some limitations. Other preexisting structures behind the heart may also mimic an extracardiac tumor. Excessive amplification degrades lateral resolution, and the size of a tumor, especially one behind the heart, may be overestimated. Any structures parallel to the ultrasonic beam do not produce clear echoes. The ultrasonic window increases with cardiac enlargement and decreases with pulmonary emphysema. Nevertheless, this technique can produce cross-sectional images of the heart and abnormal structures in the posterior mediastinum of good quality, and these images may reveal useful anatomic information including various intra- and extracardiac tumors. We consider that cross-sectional echocardiography is indicated in all patients with suspected mediastinal or esophageal tumors and that greater use of this technique will permit more frequent and earlier detection of tumors causing left atrial obstruction.

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Hemodynamic Pattern Resembling Pericardial Constriction After Acute Inferior Myocardial Infarction With Right Ventricular Infarction

DOUGLAS P. JENSEN, MD
JAMES P. GOOLSBY, Jr., MD
PHILIP B. OLIVA, MD, FACC

Denver, Colorado

Two patients with acute inferior myocardial infarction complicated by cardiogenic shock are presented. Cardiac catheterization 2 and 7 days after infarction, respectively, revealed a hemodynamic pattern resembling constrictive pericarditis. Right coronary occlusion proximal to the right ventricular marginal branches was present in both patients. Resolution of the constrictive hemodynamic pattern was demonstrated in the one survivor at repeat catheterization 7 weeks after infarction. The mechanism for constrictive hemodynamics in these patients is unclear.

The clinical and hemodynamic diagnosis of right ventricular infarction depends on evidence of predominant right ventricular failure in the setting of acute infarction.[1–4] The clinical findings usually include inferior infarction, distended neck veins, clear lungs, hypotension and heart block. The hemodynamic data indicate that mean right atrial and pulmonary arterial pressures are essentially equal, thus suggesting that the right ventricle does not generate pressure. Pathologic examination usually reveals extensive infarction involving the posterior left ventricular wall, the interventricular septum and the posterior and lateral walls of the right ventricle.[1,2,4–6]

Two patients with the clinical syndrome of right ventricular infarction are presented. At cardiac catheterization both demonstrated a hemodynamic pattern strongly resembling constrictive pericarditis. Follow-up catheterization of the one survivor 7 weeks after infarction disclosed normal hemodynamic function.

Case Reports

Case 1

This 51 year old man experienced typical angina pectoris in March 1977. In April he experienced severe crushing chest pain, nausea and diaphoresis and was admitted to Denver General Hospital. Initially, his pulse rate was 30 beats/min, and his blood pressure was unobtainable. His pulse rate increased to 60 beats/min and blood pressure to 110/60 mm Hg after the administration of atropine and isoproterenol. The jugular venous pressure was normal, the lungs were clear and there was no peripheral edema. A fourth sound gallop was present (during periods of sinus rhythm), but there was no third sound gallop or murmur.

The chest X-ray film showed normal heart size and clear lungs. The initial electrocardiogram revealed an acute inferior infarction with complete heart block and a junctional pacemaker.

The initial hours of hospitalization were characterized by multiple episodes of ventricular fibrillation, marked sinus bradycardia requiring placement of a temporary transvenous pacemaker and continued hypotension (blood pressure maintained at 85 to 90 mm Hg with fluid volume and dopamine infusion). The pulmonary arterial wedge pressure was 15 mm Hg. An intraaortic balloon was inserted.

From the Division of Cardiology, Denver General Hospital and the Department of Medicine, University of Colorado School of Medicine, Denver, Colorado. Manuscript received February 27, 1978; revised manuscript received June 13, 1978, accepted June 14, 1978.

Address for reprints: James P. Goolsby, Jr., MD, Cardiology Division, Denver General Hospital, West 8th and Cherokee Street, Denver, Colorado 80204.

Right and left heart catheterization was performed 24 hours after the clinical onset of infarction. No pericardial thickening or fluid was found as judged from the distance between the catheter and the right atrial wall and from the relation of the coronary arteries to the cardiac shadow. Hemodynamic data are presented in Table I. Striking diastolic pressure equilibration was apparent in the right atrial, right ventricular and simultaneous right and left ventricular pressure tracings (Fig. 1, A to C). Biplane left ventricular cineangiography (intraaortic balloon off) showed inferoapical hypokinesia and normal anterior wall motion. The ejection fraction was 63 percent. Coronary angiography revealed total occlusion of the right coronary artery proximal to any right ventricular marginal branch. The left anterior descending and diagonal arteries appeared normal. There was severe stenosis of the second circumflex marginal branch at its origin.

The patient's clinical and hemodynamic condition improved, and the intraaortic balloon was removed on the 4th

TABLE I

Cardiac Catheterization Data

Case no.	Date	Pressures (mm Hg) RA	RV	PA	PAW	LA	LV	CI (liters/min per m^2)
1	4/5/77	(18)	29/10–20	28/20 (23)	(17)	. . .	117/3–20	1.3
	5/25/77	(5)	25/0–9	25/11 (15)	. . .	. . .	125/0–12	3.0
2	8/13/77	(20)	31/0–19	30/20	. . .	(20)	115/0–21	2.1

Numbers in parentheses indicate mean pressures.
CI = cardiac index (determined with the Fick principle); LA = left atrium; LV = left ventricle; PA = pulmonary artery; PAW = pulmonary arterial wedge; RA = right atrium; RV = right ventricle.

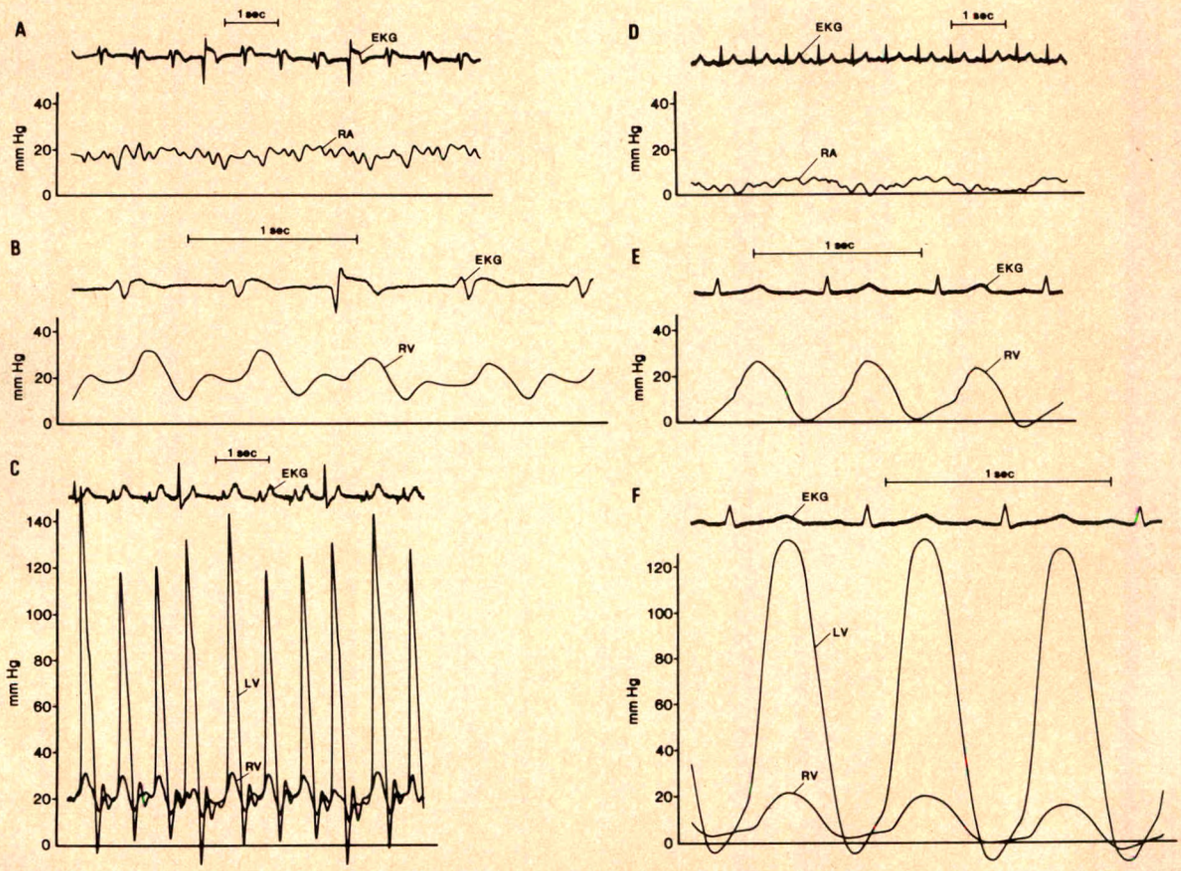
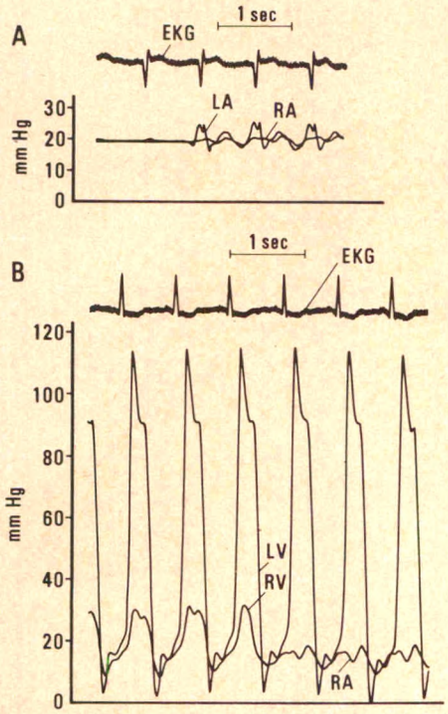


FIGURE 1. Case 1. Retouched pressure tracings comparing data from the initial **(A** to **C)** cardiac catheterization on April 5, 1977 and the repeat **(D** to **F)** catheterization on May 25. Abnormalities noted in the first study include the absence of respiratory variation in the right atrial (RA) tracing **(A),** a dip and plateau configuration in the right ventricular (RV) pressure **(B)** and diastolic equilibration of simultaneous right and left ventricular (LV) pressures with dip and plateau configuration in the latter tracing **(C).** The patient was in a paced rhythm with intermittent sinus capture at the time of the first study. The variation in peak systolic left ventricular pressure **(C)** is related to intermittent sinus capture and not pulsus paradoxus. The highest pressures occur with sinus capture beats and with the longer pauses from sinus capture to the next paced beat. The resolution of pressure abnormalities is seen in **D** to **F.** EKG = electrocardiogram.



IGURE 2. Case 2. Retouched pressure tracings obtained at cardiac atheterizaton on August 13, 1977. **A,** simultaneous mean and phasic ft and right atrial tracings. Mean pressures in the two atria are identical. , left ventricular pressure was recorded as the venous catheter was imultaneously withdrawn from the right ventricle to the right atrium. iastolic equilibration of pressures is apparent. LA = left atrium; other bbreviations as in Figure 1.

ospital day. The patient was discharged on the 21st hospital ay.

A second cardiac catheterization was performed 7 weeks fter infarction. Hemodynamic data are presented in Table . Diastolic pressure equilibration was absent in the right trial, right ventricular and simultaneous right and left ventricular pressure tracings (Fig. 1, D to F).

ase 2

This 54 year old man presented to Denver General Hospital n August 6, 1977, after 30 hours of intermittent substernal hest pain with radiation to both arms. The initial electroardiogram revealed an acute inferior myocardial infarcion.

On admission to the intensive care unit the patient's blood ressure was 140/100 mm Hg, pulse rate 82 beats/min and espiratory rate 15/min. Initially, there was no elevation of ugular venous pressure. Bibasilar rales were present. A fourth ound gallop was audible, but there was no third sound gallop r murmur. The initial chest X-ray film was normal.

On the 3rd hospital day the patient became oliguric, and is blood pressure decreased gradually to 80/50 mm Hg. wan-Ganz catheterization revealed a mean right atrial ressure of 10 mm Hg with a prominent *y* descent and little espiratory variation. Pulmonary arterial pressure was 24/10 m Hg (mean 14) and mean pulmonary arterial wedge pressure 10 mm Hg. Intravenous fluid was infused to increase ulmonary arterial wedge pressure to 15 to 18 mm Hg, reulting in the normalization of blood pressure and urinary utput.

Cardiac catheterization was performed on the 7th hospital day because frequent prolonged episodes of severe chest pain recurred. Table I presents the hemodynamic data. Figure 2, A and B, shows the diastolic pressure plateau seen with simultaneously recorded left and right heart pressures. No pulsus paradoxus was recorded. Biplane left ventricular cineangiography revealed severe inferior wall and mild anterior wall hypokinesia. The ejection fraction was 42 percent. Coronary angiography revealed total occlusion of the right coronary artery proximal to any right ventricular marginal branch. The left main coronary artery was 50 to 75 percent narrowed, the left anterior descending artery was small and diffusely narrowed and the circumflex artery was severely obstructed before the origin of the two marginal branches.

Episodic chest pain continued without enzyme evidence of further myocardial necrosis. Attempted insertion of an intraaortic balloon was unsuccessful because of peripheral vascular disease. On the 10th hospital day coronary bypass surgery was performed because of continued chest pain. No pericardial effusion or thickening was noted. Right ventricular contractility appeared very poor, but left ventricular contractility was fair. The only graftable vessels were the left anterior descending and diagonal vessels. The patient could not be weaned from cardiopulmonary bypass despite the use of vasopressors and the insertion of an intraaortic balloon into the ascending aorta.

Discussion

Hemodynamic pattern of pericardial constriction: The pressure recordings from these two patients suggest pericardial constriction because (1) the right atrial pressure curve does not indicate respiratory variation, (2) a diastolic "dip and plateau" configuration is present in both the right and the left ventricular pressure tracings, and (3) there is equilibration of mean right atrial, right ventricular diastolic, pulmonary arterial diastolic, mean left atrial (or wedge) and left ventricular diastolic pressures. No pericardial disease was present in Case 2 at operation. In Case 1 hemopericardium due to a limited myocardial rupture or pacemaker perforation of the right ventricle cannot be excluded. However, the absence of pulsus paradoxus makes pericardial tamponade due to hemopericardium unlikely. Reversibility of the abnormal hemodynamics in Case 1 makes chronic constrictive pericarditis an unlikely diagnosis.

Right ventricular failure: Cardiogenic shock in these two patients with only mild (Case 1) or moderate (Case 2) left ventricular dysfunction suggests that the predominant hemodynamic abnormality was right ventricular dysfunction. Both cases had evidence of right ventricular failure (high right atrial and right ventricular early and end-diastolic pressures) as well as minimal generation of pressure by the right ventricle (little increase in mean pressure from the right atrium to the pulmonary artery).

Diastolic pressure equilibration in right ventricular infarction: The frequency of diastolic pressure equilibration in acute right ventricular infarction is unknown. In most cases the mean right atrial pressure is higher than the mean pulmonary wedge pressure.[1,2] Only one of six patients in the series of Cohn et al.[1] had equal right atrial and pulmonary wedge pressures.

Raabe and Chester[4] reported a case of right ventricular infarction in which volume loading produced diastolic pressure equilibration. A diastolic dip and plateau contour was also present in the right ventricular pressure curve. It is possible that constrictive hemodynamics may be a more frequent finding after volume loading in patients with right ventricular infarction (intravenous fluid was infused in both of our patients before catheterization). The mechanism for constrictive hemodynamics in these patients is unclear.

We were unable to find any previous report of coronary arteriograms in patients with acute inferior infarction and right ventricular involvement. Both of our patients had occlusion of a dominant right coronary artery proximal to the origin of any right ventricular marginal branch. Wade[5] reported occlusion of the right coronary artery in 18 of 19 hearts with right ventricular infarction examined at autopsy but did not specify the point of occlusion.

Prognosis: Reversibility of the constrictive hemodynamics was documented in Case 1 by recatheterization 7 weeks after infarction. Four of six patients reported on by Cohn et al.[1] survived right ventricular infarction and shock. The prognosis appears to be better than cardiogenic shock after anterior myocardial infarction. Recognition of this syndrome is important because fluid therapy, with or without pharmacologic or mechanical unloading of the left ventricle, may be instrumental in improving cardiac function and survival.

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Fortuitous Rupture of Aortic Aneurysm: A Catastrophic Event Affording Time for Surgical Cure

JAMES B. YOUNG, MD
JOHN O. F. ROEHM, Jr., MD
GERALD M. LAWRIE, MD, FACC
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JIMMY F. HOWELL, MD, FACC
RAFAEL ESPADA, MD, FACC
RICHARD R. MILLER, MD, FACC

Houston, Texas

The rupture of an aortic aneurysm is generally a fatal event, but occasionally the rupture will occur into an adjacent vascular structure, thereby preventing exsanguination and affording temporary survival. Three cases are presented illustrating the fortuitous nature of the rupture of an aortic aneurysm into a vascular structure. The first patient had an atherosclerotic abdominal aortic aneurysm that ruptured into the inferior vena cava and was successfully repaired. The second case demonstrates the formation of a fistula from the aorta to the left pulmonary artery in a patient with a syphilitic thoracic aortic aneurysm. In the third patient a dissecting aneurysm of the aortic root that communicated with the right ventricle after coronary bypass surgery was successfully repaired. Rarely, aortic aneurysms will rupture fortuitously into vascular capacitance structures. These three cases emphasize the need for early accurate diagnosis and the institution of appropriate surgical measures.

An awareness of the dramatic complications of aortic aneurysms extends back many centuries. Fernel[1] in 1581 called attention to the capacity of internal arteries to dilate abnormally, forming structures "... full of spirituous and blood," Ambroise Paré[2] in the late 16th century vividly described a ruptured thoracic aortic aneurysm occurring in a tailor who "... whilest he was playing at tennis fell dead, the (arterious) vessel having broken: his body being opened I found a great quantity of blood poured forth into the capacity of the chest; the artery dilated to that largeness as to hold a man's fist, and the inner coat thereof was bony."

Rupture of an aortic aneurysm is a dramatically catastrophic event. The reason for resection of this dilation is to prevent rupture and other well known complications such as dissection, embolization of clot, selective arterial occlusion, pain and vital organ obstruction. Aneurysms can rupture into the thoracic cavity, the bronchi, the pericardium, the right or the left ventricle, the abdomen, the retroperitoneal space and the bowel, as well as into adjacent veins and arteries. If, fortuitously, an aneurysm ruptures into a venous or arterial system, creating an arteriovenous, arterioarterial or arterioventricular fistula, life may be temporarily sustained, and life-saving procedures may be instituted. The physician must be aware of the different types of fortuitous rupture of an aortic aneurysm in order to intervene effectively.

The three case reports presented illustrate, respectively, the formation of arteriovenous, arterioarterial and arterioventricular fistula secondary to the rupture of aortic aneurysms. These cases emphasize the need to suspect the diagnosis early if surgical intervention is to be successful.

Case Reports

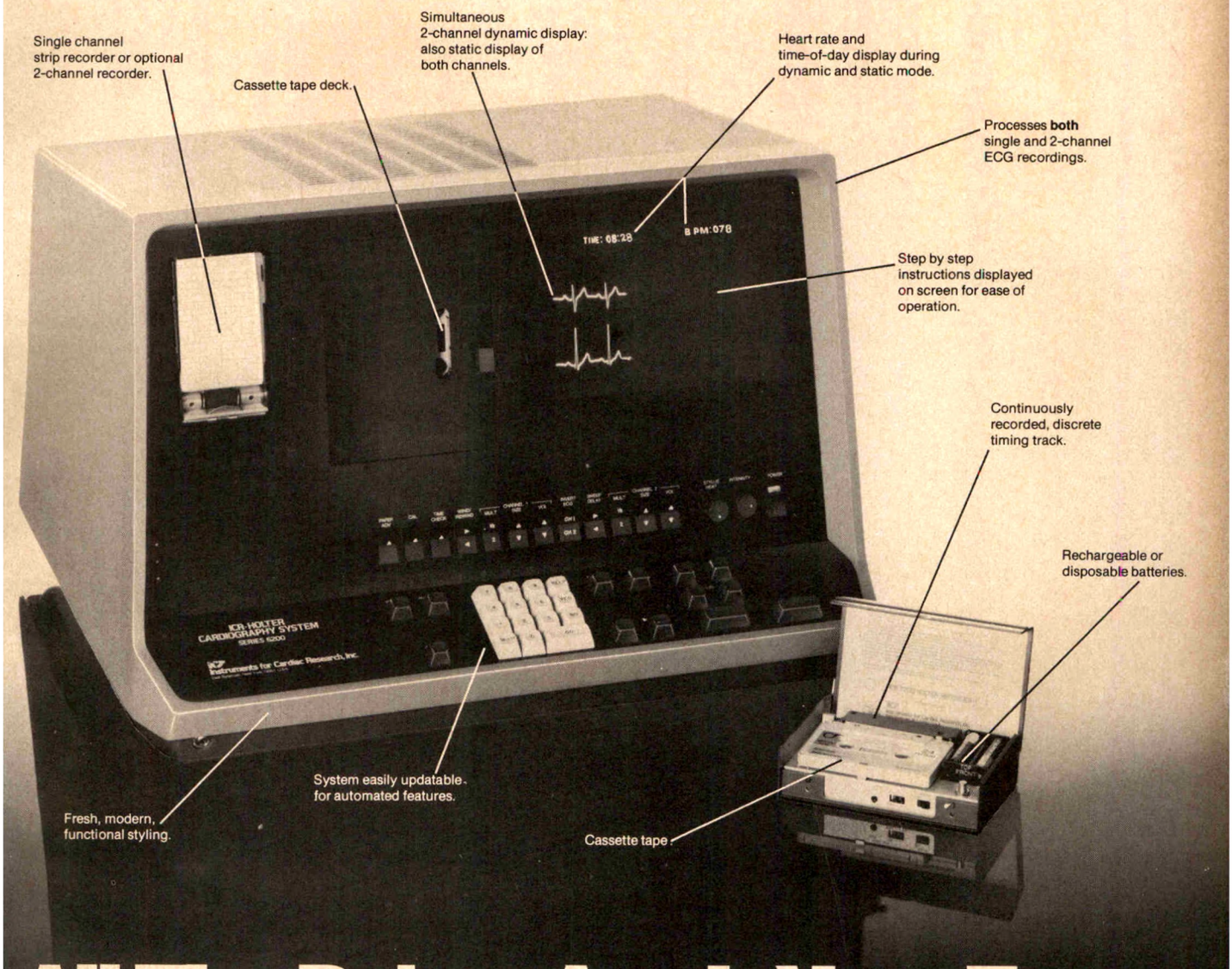
Case 1

A 70 year old man referred for evaluation of possible renal vein thrombosis presented to The Methodist Hospital complaining of extreme fatigue. Sixty days

From the Section of Cardiology, Departments of Medicine, Radiology and Surgery, Baylor College of Medicine, Houston, Texas. This study was supported in part by Grant HL-17269 from the National Heart, Lung and Blood Vessel Research and Demonstration Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received March 28, 1978; revised manuscript received June 6, 1978, accepted June 7, 1978.

Address for reprints: James B. Young, MD, Section of Cardiology, Baylor College of Medicine, The Methodist Hospital, 6516 Bertner Boulevard, M.S. 412, Houston, Texas 77030.

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"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

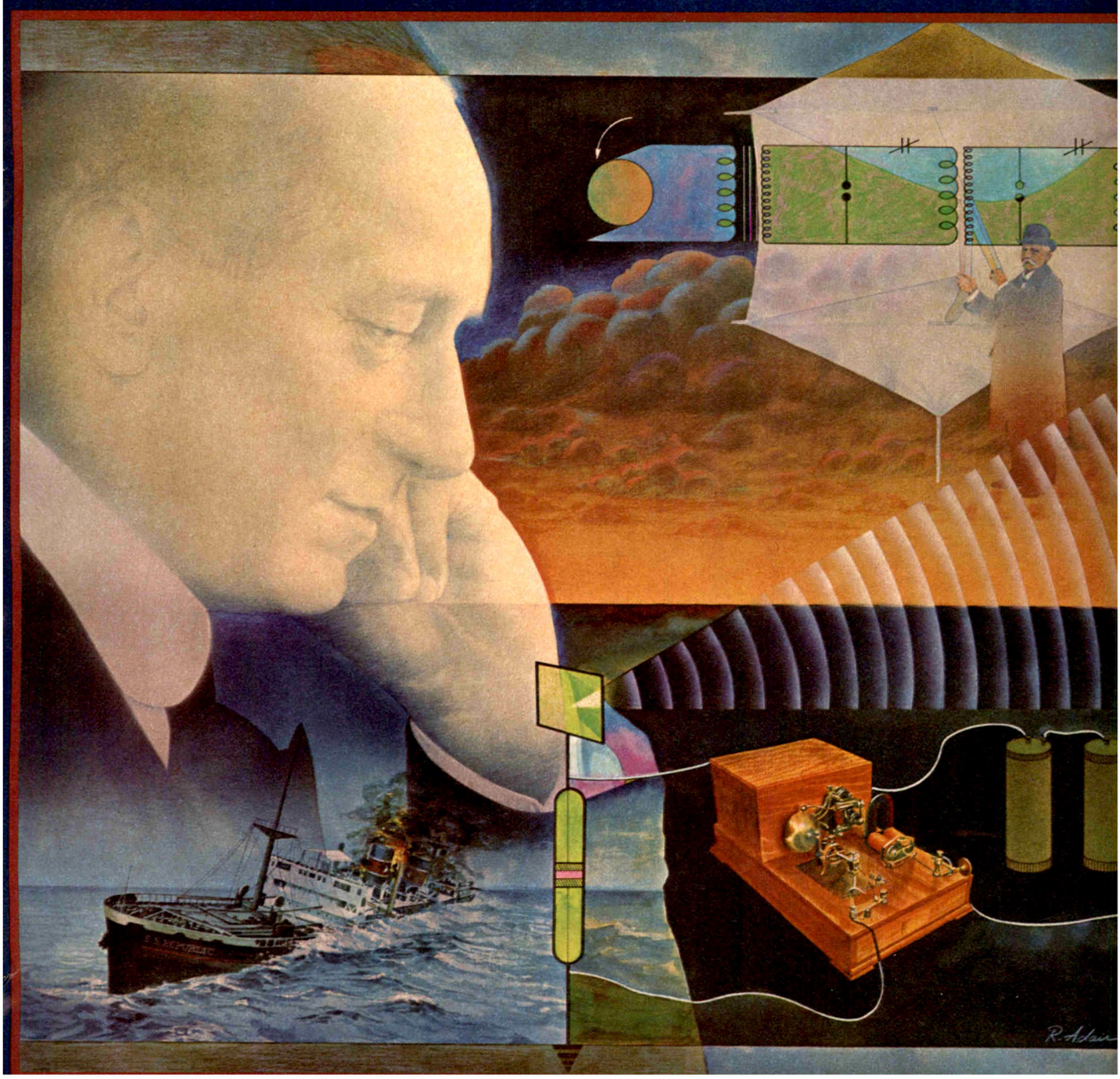
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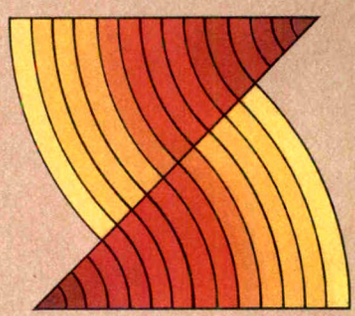
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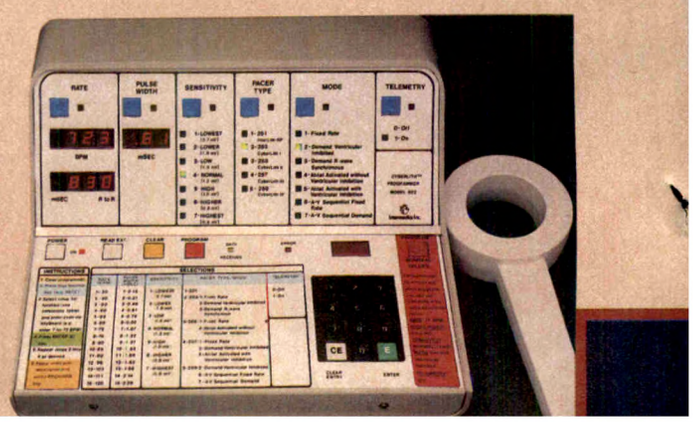
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The Guglielmo Marconi original water color shown on the first page of this ad is the second in a series commissioned by Intermedics. A limited-edition print, numbered and signed by artist Ron Adair, is being made available by Intermedics to physicians only. To obtain your print please write to Marketing Administration, Intermedics, Inc., P.O. Box 617, Freeport, Texas 77541.

Note:
The CyberLith is currently undergoing clinical evaluation and is not routinely available on a commercial basis.

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Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and relatively widely variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Microwave ovens that do not exceed federal guidelines for leakage (0.5 mW/cm^2 at 2.5 cm from the appliance) will not affect the pacemaker, but leakage in excess of that amount may cause interference. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

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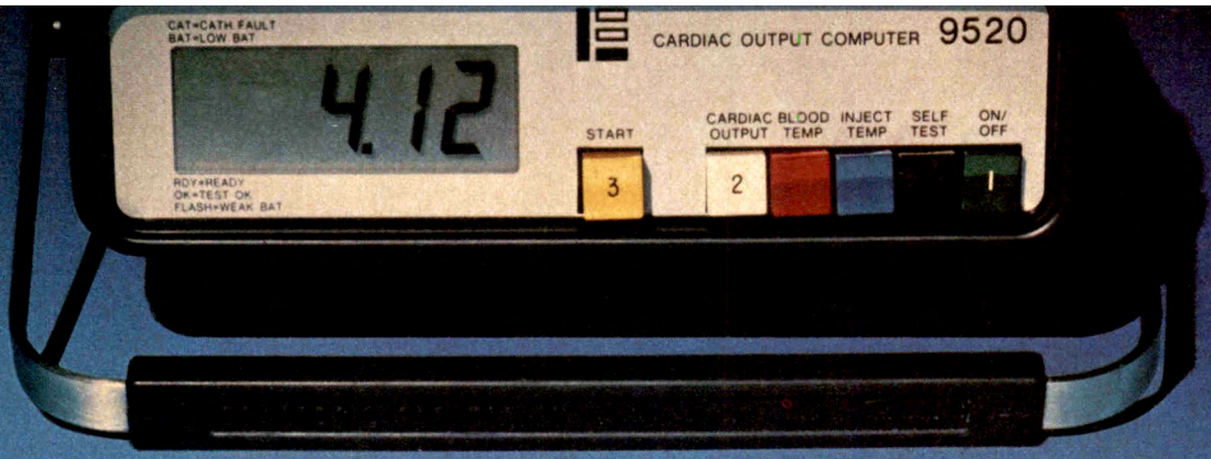
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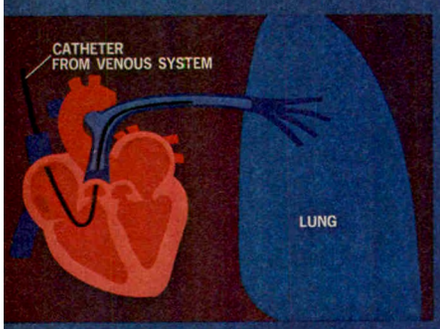
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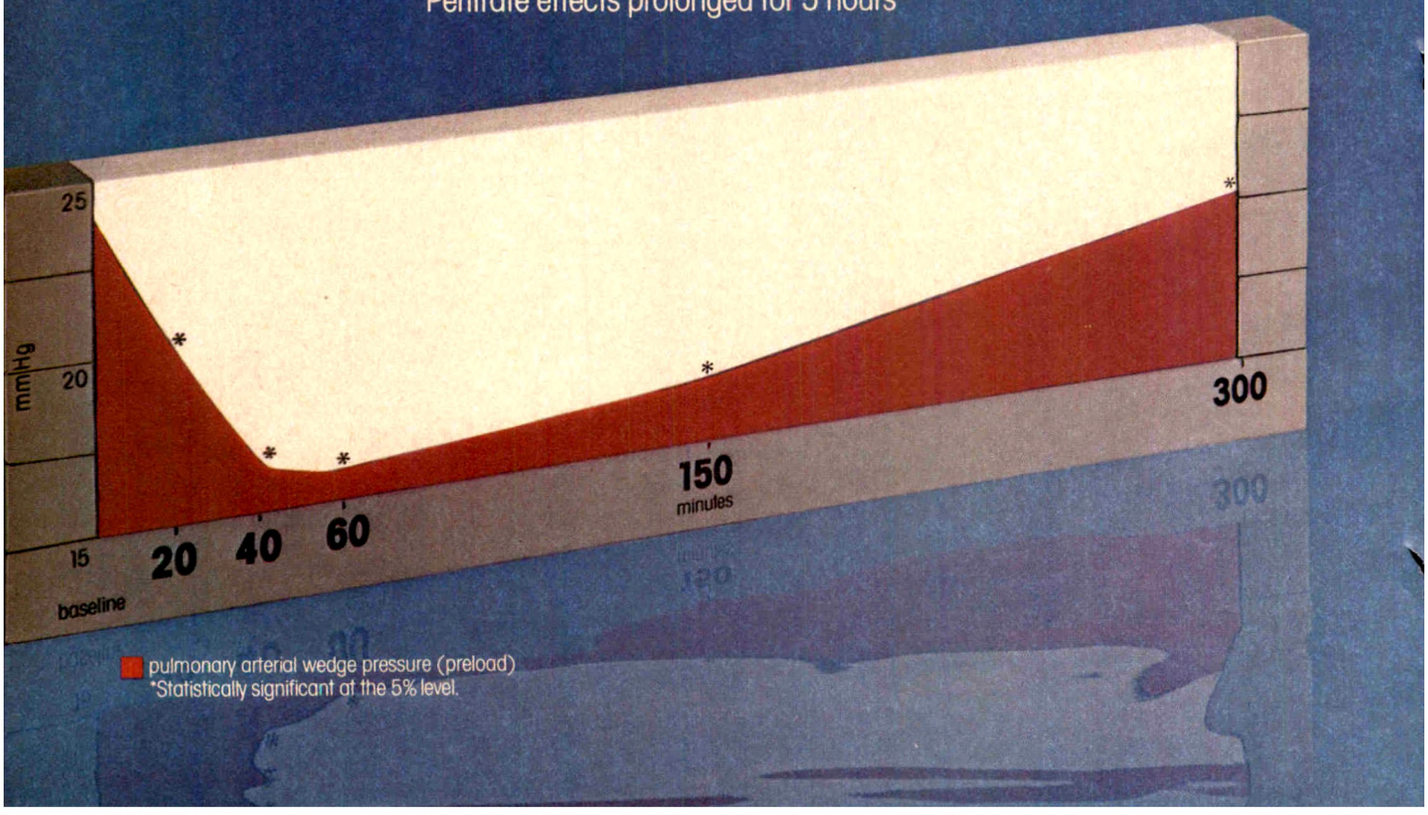
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In a randomized double-blind study of catheterized patients with congestive heart failure, Peritrate 40 mg demonstrated marked changes in a variety of hemodynamic parameters with no change in heart rate.[1]

A marked reduction in PRELOAD: Peritrate reduced pulmonary arterial wedge pressure for over 300 minutes. The maximum reduction was 37%. Pulmonary arterial mean pressure was also reduced for over 300 minutes. These manifestations of reduced PRELOAD resulted from an increase in venous capacitance leading to a reduction in left ventricular end-diastolic volume and pressure. The observed reduction in pulmonary wedge pressure indicates marked preload reduction.

Peritrate effects prolonged for 5 hours



A reduction in AFTERLOAD: A significant reduction of arterial blood pressure, correlating with reduced AFTERLOAD, was maintained for over 300 minutes.[1]

Reduction in blood pressure for 5 hours

parameter	before Peritrate n=12	60 minutes after Peritrate n=12	150 minutes after Peritrate n=12	300 minutes after Peritrate n=8
blood pressure (mmHg) systolic	122.6	116.7*	116.9	116.8*
diastolic	68.7	63.4*	61.3*	61.0*

*Statistically significant at the 5% level.

Peritrate actions observed

- Activity was prolonged for at least 5 hours.
- PRELOAD and AFTERLOAD showed a marked reduction lasting at least 5 hours.

1. Klein RC, Amsterdam EA, Pratt C, et al: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy. Presented at The American Federation for Clinical Research, San Francisco, Calif, April 29-May 1, 1978.

Please see following page for brief summary of prescribing information.

Conclusions

1. The prolonged reduction in preload and afterload reduces the amount of energy expended and oxygen consumed by the heart. This reduction in oxygen demand should relieve or prevent angina.
2. Provides a smooth onset of action without tachycardia. Unwanted effects are rare, and patient compliance is excellent.

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Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.
In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:
(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.
Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).
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Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).
Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).
STORE BETWEEN 59° and 86° F (15° and 30° C).
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Full information is available on request.

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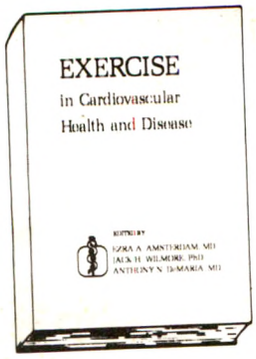
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Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

SEPTEMBER 1977, 408 PAGES, ILLUS.

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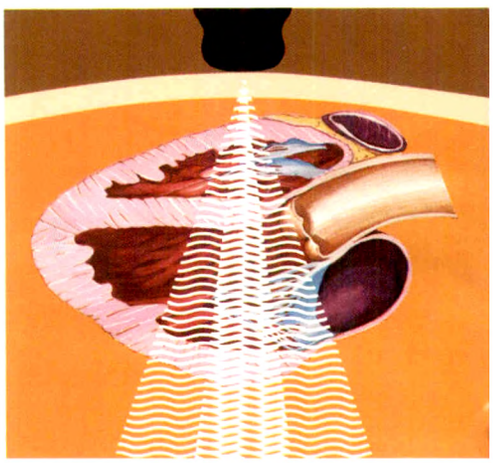
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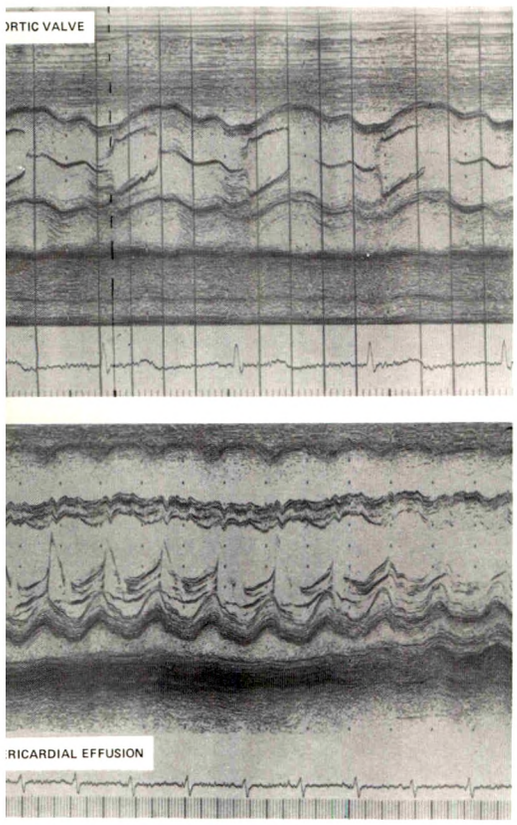
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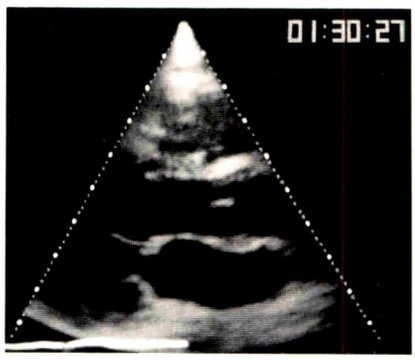
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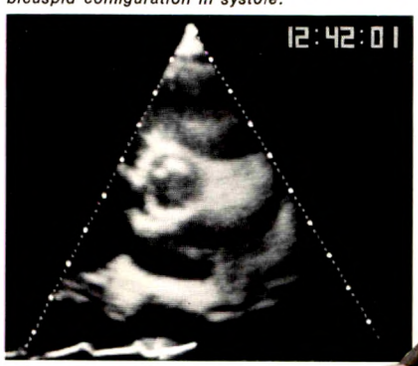


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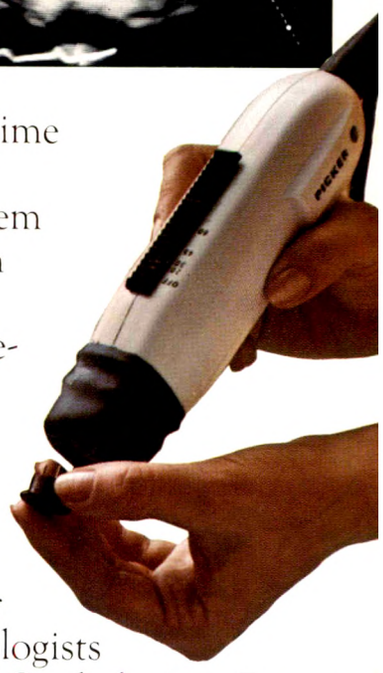
Long axis view of left ventricle and aortic root.



Short axis view of aortic valve showing bicuspid configuration in systole.



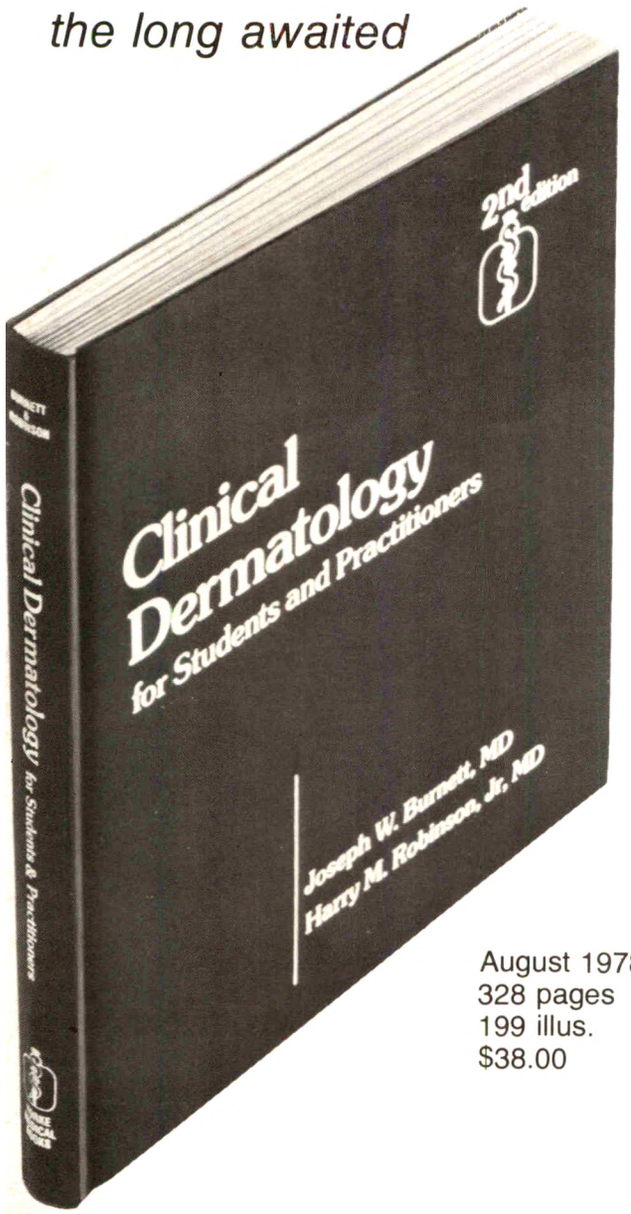
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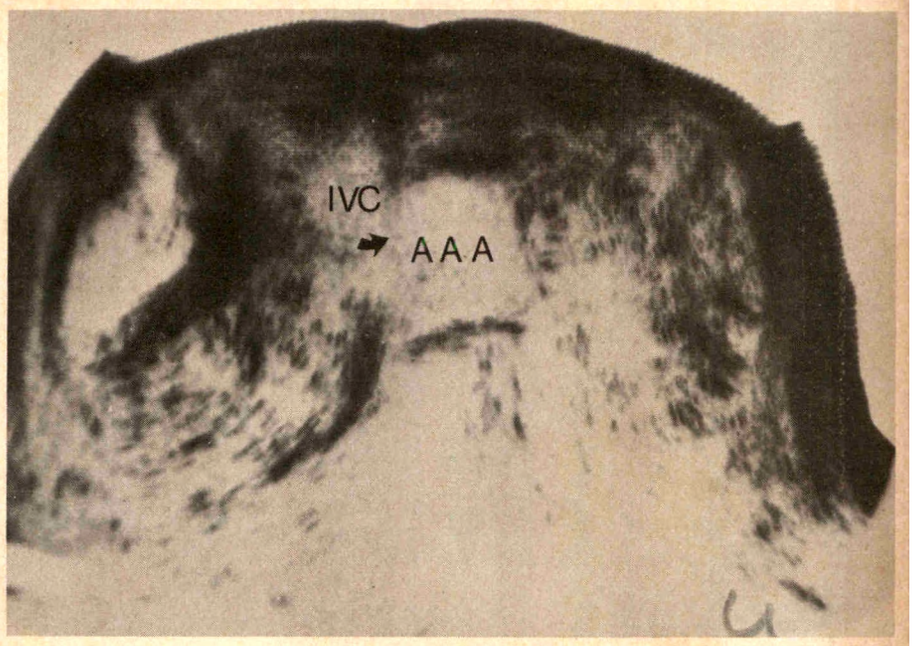


FIGURE 1. Case 1. Abdominal sonogram at the level of the umbilicus, demonstrating a dilated abdominal aorta (AAA) and inferior vena cava (IVC) with an aneurysm and an aortocaval fistula. **Arrow** points to the region of the fistula formation.

before admission he had had sudden, excruciating, nonradiating pain in the left upper quadrant, left flank and mid abdominal areas, together with near syncope and palpitations. He was hospitalized, and during the next 48 hours the pain gradually abated with the use of narcotics. During the subsequent 30 day hospitalization, congestive heart failure and renal insufficiency developed, and there was an increase in blood urea nitrogen to 59 mg/100 ml and serum creatinine to 2.6 mg/100 ml. An intravenous pyelogram failed to demonstrate a left kidney, and a left flank mass was palpated; because of persisting symptoms and abnormal renal function, the patient was referred to The Methodist Hospital.

Presenting vital signs revealed a wide pulse pressure (blood pressure 140/50 mm Hg), sinus tachycardia (110 beats/min) and tachypnea. Tense jugular veins distended to the angle of the jaw, and rapidly collapsing carotid pulses that had an increased rate of rise and amplitude were noted. Auscultation of the chest revealed fine basilar rales, an elevated poorly moving diaphragm and a grade 2/6 harsh continuous murmur in the lower posterior thorax. Examination of the heart revealed that the first heart sound was normal and the second was normally split but accentuated; a loud third sound gallop was heard. There was no cardiac murmur. An 8 cm pulsating mass was noted at the level of the umbilicus, with a palpable grade 4/6 continuous bruit. Pitting edema of both lower limbs extended up to the umbilicus with clear demarcation at that point. Peripheral pulses in the upper limbs were bounding, the femoral pulses were diminished, and the pedal pulses were not palpable. There was no evidence of superficial venous collateral circulation.

Chest roentgenograms revealed eventration of the left hemidiaphragm, pulmonary vascular congestion and a normal cardiac silhouette. The electrocardiogram demonstrated sinus tachycardia and nonspecific ST-T wave changes. A lateral abdominal X-ray film revealed an abdominal aortic aneurysm 7 cm in diameter. An abdominal sonogram (Fig. 1) confirmed the aortic aneurysm and disclosed marked dilation of the inferior vena cava, suggesting an aortoinferior vena caval fistula. Abdominal aortography (Fig. 2) demonstrated a fistulous shunt with a large volume between the infrarenal aneurysmal aorta and the inferior vena cava. The left kidney did not opacify.

Excision of the abdominal aortic aneurysm and ligation of the fistulous communication between the aorta and inferior vena cava were accomplished without complication. Postoperatively spontaneous diuresis occurred, with resolution of the massive edema in the lower limbs. Dyspnea dis-

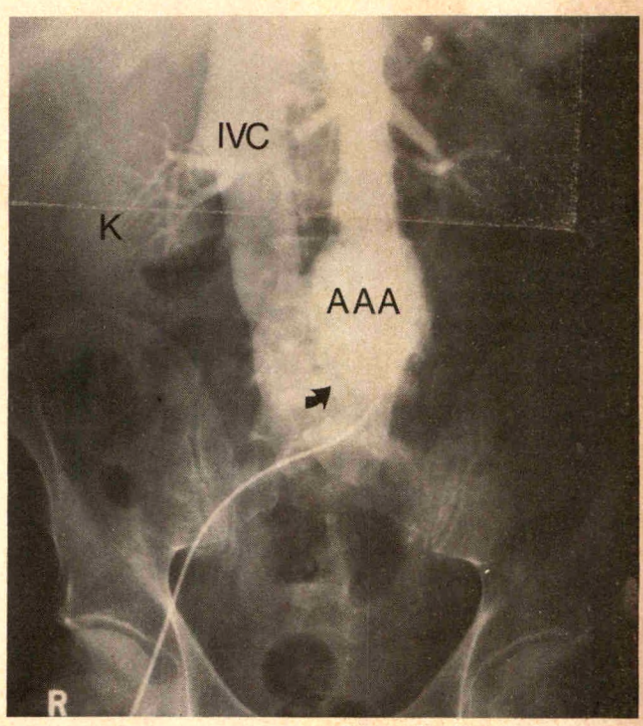
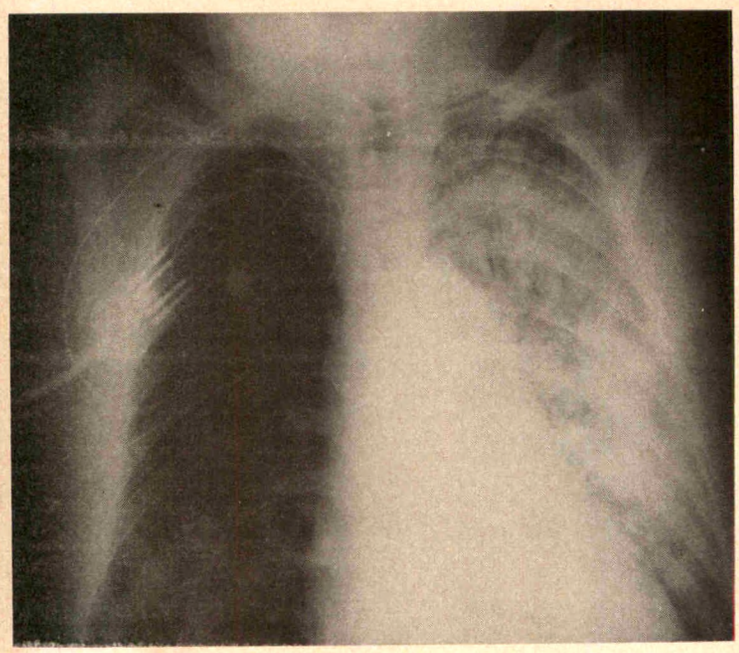
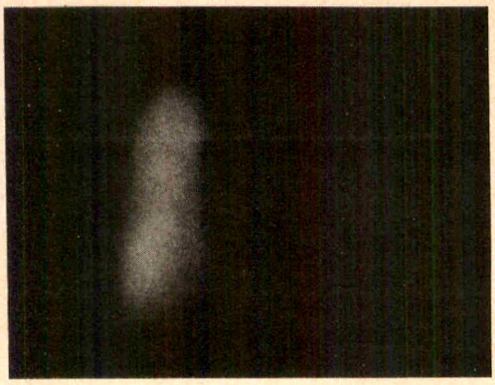
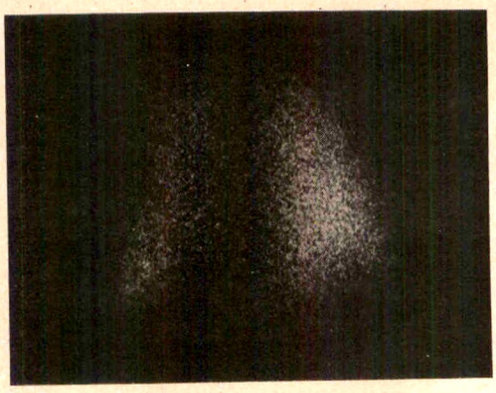


FIGURE 2. Case 1. Aortogram showing an infrarenal aortic aneurysm (AAA) with a fistulous communication to the inferior vena cava (IVC). Both renal arteries are patent. K = right kidney; the **arrow** points to the region of the fistula formation.





A (left) PERFUSION SCAN Posterior View (right)



B (left) VENTILATION SCAN Posterior View (right)

FIGURE 3, left. Case 2. Portable anteroposterior chest roentgenogram demonstrating left-sided, unilateral pulmonary edema.

FIGURE 4, right. Case 2. **A,** posterior view of a perfusion lung scan demonstrating the absence of perfusion of the right lung secondary to obstruction of the right pulmonary artery by the aneurysm. **B,** ventilation of the right lung can be seen in the posterior view ventilation scan.

appeared and laboratory indexes of renal function returned to normal.

Case 2

This 68 year old man was transferred to The Methodist Hospital for evaluation and treatment of refractory congestive heart failure. Four years before admission a syphilitic ascending aortic aneurysm had been diagnosed. Except for easy fatigability, the patient had been essentially asymptomatic until 28 days before admission, when he experienced the sudden onset of severe, sharp, nonradiating left anterior chest pain that persisted for 5 hours. Because of progressive dyspnea he was admitted to a local hospital 72 hours after the onset of symptoms; he received a digitalis glycoside, diuretic drugs, hydalazine and nitroglycerine paste. He was then transferred to The Methodist Hospital.

On admission, a wide pulse pressure (blood pressure 140/40 mm Hg) and sinus tachycardia (heart rate 100 beats/min) were present. Significant physical findings included normal jugular venous pulsation and bounding carotid pulses. There was cardiomegaly; a grade 4/6 systolic ejection murmur and a grade 2/6 diastolic rumble were heard at the apex. Breath sounds were diminished bilaterally, and percussion was dulled at the left lung base.

Significant laboratory data revealed prerenal azotemia and normal serum cardiac enzymes. Chest roentgenograms demonstrated a large calcified aneurysm of the ascending aorta, cardiomegaly, a left pleural effusion and pulmonary vascular congestion of the left lung only (Fig. 3). The electrocardiogram revealed sinus rhythm with a prolonged P-R interval and diffuse ST-T wave depression. On thoracentesis, 900 cc of serosanguinous fluid was obtained from the left side of the chest.

Because of the history of chest pain, dyspnea, hemoptysis, arterial hypoxemia (blood gases: partial pressure of oxygen 49 mm Hg and of carbon dioxide 30 mm Hg) and bloody effusion, pulmonary embolism was suspected in addition to a syphilitic aortic aneurysm with aortic insufficiency. A ventilation and perfusion lung scan demonstrated the absence of perfusion in the right lung and normal perfusion and ventilation of the left (Fig. 4).

Pulmonary angiography and aortography were performed, demonstrating a fusiform ascending aortic aneurysm with a posterior saccular aneurysm arising from it. The latter completely obstructed the right pulmonary artery and communicated with the main pulmonary artery (Fig. 5). Main pulmonary arterial pressure was 80/30 mm Hg (mean 45) and was identical to aortic pressure. There was no aortic insufficiency.

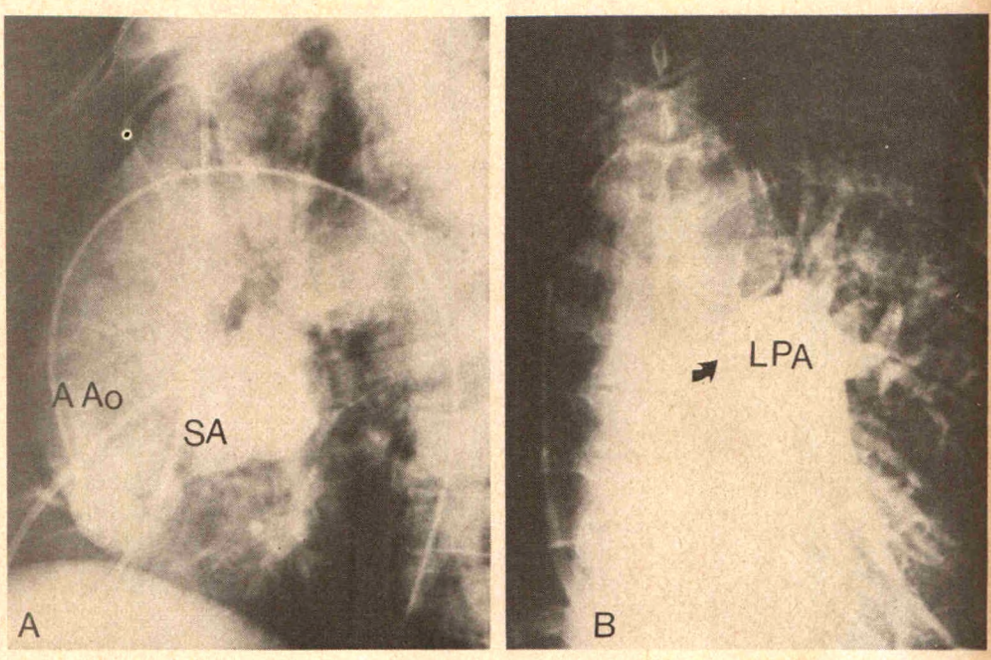


FIGURE 5. Case 2. **A,** lateral projection of a thoracic aortogram demonstrating a fusiform ascending aortic aneurysm (A Ao) with a saccular projection of the aneurysm (SA) over the right pulmonary artery. The fistula between the saccular aneurysm and the pulmonary artery produces opacification of the pulmonary artery. **B,** anteroposterior projection of a pulmonary angiogram shows no visible flow through the right pulmonary artery. LPA = left pulmonary artery; the **arrow** points to obstruction of the right pulmonary artery.

Because of the patient's rapidly deteriorating condition, he was taken directly to the operating room where, despite the surgical closure of the aorta-pulmonary arterial fistula and resection of the saccular aortic aneurysm, he could not be weaned from cardiopulmonary bypass and died.

Case 3

This 53 year old man was referred to The Methodist Hospital for evaluation of a new diastolic murmur and worsening heart failure. Four years previously he had had successful saphenous vein-coronary bypass grafting to the left anterior descending and circumflex coronary arteries. Sixty days before admission he suddenly experienced sharp, severe, steady, nonradiating precordial chest pain that terminated in a syncopal episode. The patient was hospitalized, and his pain abated with morphine. A previously unrecorded diastolic murmur was detected, and a subendocardial myocardial infarction was diagnosed. Congestive heart failure developed and was slightly alleviated with the administration of diuretic drugs and digitalis. Over the ensuing 6 weeks heart failure progressed to functional class IV,[3] and progressive hoarseness appeared.

On admission, sinus tachycardia (100 beats/min), tachypnea and wide pulse pressure (blood pressure 170/70 mm Hg) were present. Significant physical findings included jugular venous distension with increased amplitude of both the A and V waves and bounding carotid pulses. The lungs were clear. There was cardiomegaly, a hyperdynamic apical pulse and a prominent right ventricular impulse. The first heart sound was normal and the second widely split, with a summation gallop at the apex. A grade 3/6 decrescendo diastolic murmur was heard along the right lower sternal border with a grade 1/6 short nonradiating systolic ejection murmur noted at the right upper sternal border. The peripheral pulses were bounding, and there was no peripheral edema. The left vocal cord moved poorly at laryngoscopy.

Chest roentgenograms showed left ventricular enlargement and a widened mediastinum. The electrocardiogram showed left ventricular hypertrophy with a strain pattern, and the echocardiogram showed mild aortic root and right ventricular

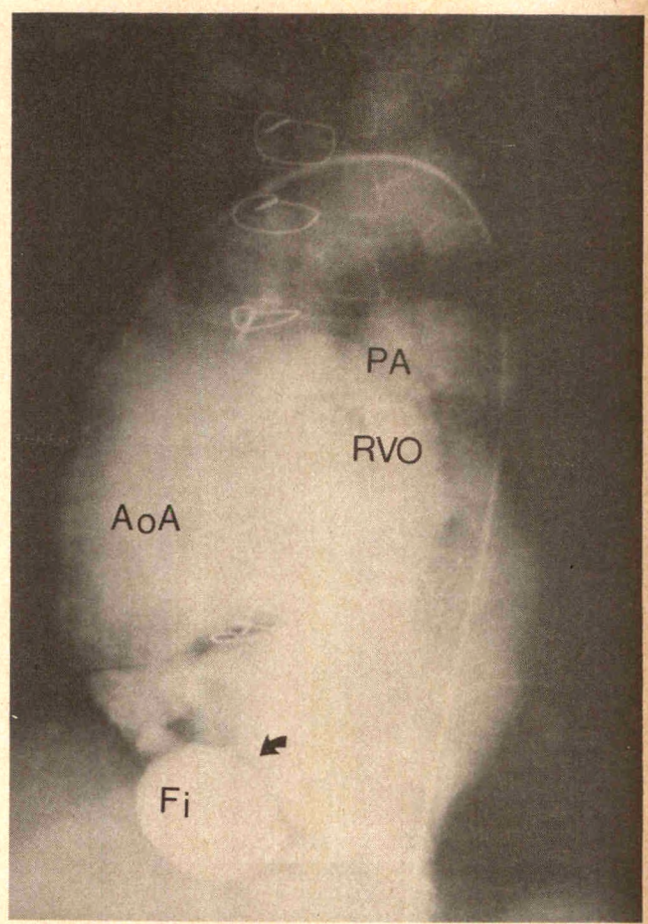


FIGURE 6. Case 3. Aortic root injection demonstrating a dissecting thoracic aortic aneurysm (AoA) confined to the ascending aorta with fistulous connection (Fi) from the aorta to the right ventricle. PA = pulmonary artery; RVO = right ventricular outflow tract; the **arrow** points to the communication between the right ventricle and the fistulous tract.

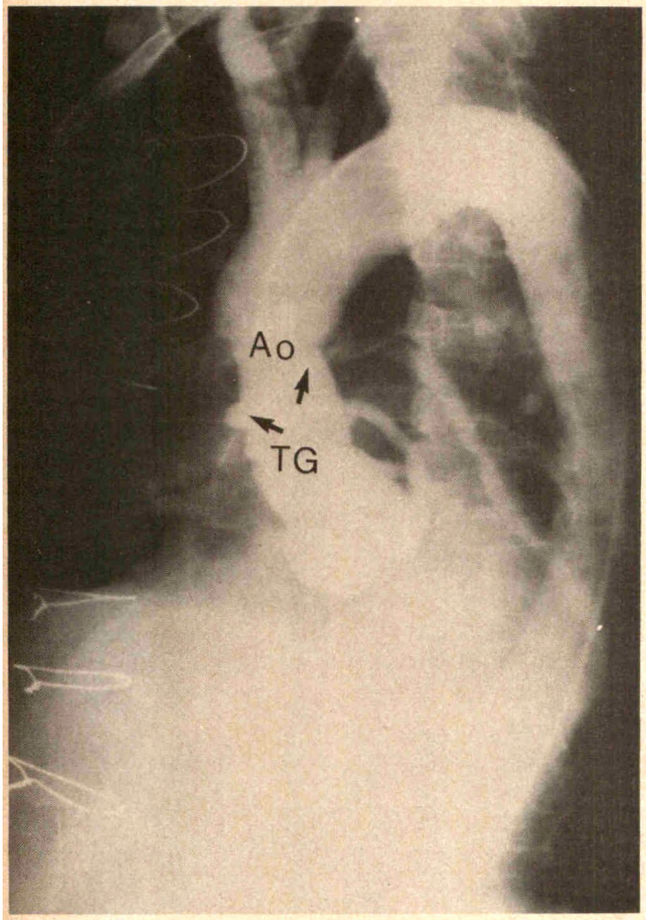


FIGURE 7. Case 3. Postoperative aortography demonstrating the successful resection of the aortic aneurysm and replacement with a Dacron tube graft (TG). The saphenous vein bypass grafts to the coronary arteries remain patent, and the fistulous communication has been closed. Ao = aorta; **arrows** point to saphenous vein implants into the graft.

dilatation with paradoxical motion of the interventricular septum.

Cardiac catheterization demonstrated abnormal hemodynamics with a pulmonary capillary wedge pressure of 38 mm Hg, left ventricular end-diastolic pressure of 40 mm Hg, pulmonary arterial pressure of 45/20 mm Hg and right atrial pressure of 7 mm Hg. Aortic root dye injection (Fig. 6) revealed a large dissecting thoracic aortic aneurysm confined to the ascending aorta, with a fistulous connection from the aorta to the right ventricle. Neither patent vein grafts nor aortic insufficiency was noted.

At surgery, a large ascending dissecting aortic aneurysm extended anteroinferiorly over the right ventricle. At the level of the proximal right coronary artery, there was a fistulous communication with the right ventricle where dissection, erosion and rupture had occurred. The coronary bypass grafts were patent. The aneurysm was resected and the fistula oversewn. Tube graft interposition and replacement of the ascending aorta was accomplished, and the coronary bypass grafts were reimplanted into the Dacron® tube.

Postoperatively, the patient's heart failure and hoarseness resolved, and aortography (Fig. 7) revealed a satisfactory postoperative graft appearance, successful closure of the aorta-right ventricular fistula and patent coronary bypass grafts.

Discussion

These three cases of fortuitous rupture of aortic aneurysm are unusual, and the hemodynamic consequences afforded prolonged survival compared with most perforations of aortic aneurysms, thereby allowing sufficient time for proper diagnosis and surgical correction. Two of our patients survived surgical intervention.

Aorta-inferior vena caval fistula due to abdominal aortic aneurysm: In a long-term surgical experience with 1,400 abdominal aortic aneurysms, Beal et al.[4] noted that 130 patients (9 percent) presented with prior rupture, including 4 whose aneurysm had ruptured directly into the inferior vena cava. The mortality rate was 34 percent in patients presenting with free rupture of an aortic abdominal aneurysm, compared with a 100 percent surgical survival rate in the four patients with an aorta-inferior vena caval communication. These findings indicate that rupture of an abdominal aortic aneurysm into the inferior vena cava may be compatible with short-term survival and thus emphasize the importance of prompt preoperative diagnosis.

The spontaneous rupture of an abdominal aortic aneurysm directly into the inferior vena cava is rare; however, aorta-inferior vena caval fistulas caused by trauma or surgery on the lumbar spine occur more frequently. Spontaneous aorta-inferior vena caval communication is accompanied by the sudden onset of back or flank pain that may gradually disappear. Signs and symptoms of attendant high output heart failure may then appear. In the special circumstance of an aorta-inferior vena caval fistula, massive edema of the lower limbs extending to the umbilicus results from abnormally elevated pressure in the inferior vena cava. Renal blood flow may decrease, causing the development of prerenal azotemia.[5] The elevated pressure in the inferior vena cava and the accelerated flow may promote renal vein thrombosis, leading to proteinuria and hematuria.[6] The large arteriovenous fistula produces physical findings consistent with a large left to right shunt, including a hyperdynamic cardiovascular state with a widened pulse pressure, bounding pulses, a pulsatile abdominal mass and a widely radiating continuous bruit heard over the mass.

In addition to the standard lateral radiograph of the abdomen, which permits the correct diagnosis of abdominal aortic aneurysm in 75 percent of cases, an abdominal sonogram will demonstrate aortic aneurysms[7,8] and suggest fistula formation when the inferior vena cava is dilated. Catheterization and aortography are required to define anatomic detail and quantify the shunt.

Aorta-pulmonary arterial fistula due to rupture of thoracic aortic aneurysm: Although abdominal aortic aneurysms that rupture are virtually always atherosclerotic in origin, rupturing aneurysms in the thoracic aorta may frequently be syphilitic. A large saccular syphilitic aneurysm may cause respiratory obstruction, hoarseness, dysphagia, neurologic symptoms, thromboembolism with ischemic complications and congestive heart failure secondary to aortic insuf-

ficiency.[9] Compression of the main pulmonary arteries has also been reported, creating significant pulmonary hypertension and segmental pulmonary oligemia with resultant ventilation/perfusion imbalance and hypoxia.[10,11] The development of a fistula between the aorta and the pulmonary artery is rare, although it was somewhat more common in the past, when syphilitic heart disease was encountered more frequently.[12] Over a 30 year period (1911 to 1941) at Charity Hospital in New Orleans, the incidence rate of rupture of the aortic aneurysm into the pulmonary artery was 0.91 percent of all thoracic aortic aneurysms and 1.83 percent of all ruptured thoracic aortic aneurysms.[13] Because syphilitic aortitis and consequent aneurysms occur less often now, spontaneous aortopulmonary fistulas are extremely rare and are usually recognized only at autopsy.

Aortic aneurysms that rupture into the pulmonary artery usually present with insidious obstruction of the pulmonary artery.[14] When a fistulous communication ultimately occurs, high output cardiac failure rapidly ensues, together with a further increase in right heart pressure. In addition to the findings related to a large ascending aortic aneurysm, the presence of a harsh murmur or bruit, at times with a to and fro pattern, a hyperdynamic circulatory state and a precordial thrill should suggest rupture into the pulmonary artery. The appearance of right axis deviation on electrocardiography or combined right and left ventricular hypertrophy should arouse suspicion that pulmonary hypertension exists. The severe hemodynamic sequelae of a large left to right shunt may be refractory to medical therapy and usually result in rapid deterioration and death unless surgical correction is accomplished.

Aorta-right ventricular fistula: Rupture of thoracic aneurysms into the right ventricle is extraordinarily uncommon. Manipulation of the ascending aorta during coronary arterial-saphenous vein bypass surgery may result in an intimal tear with late formation of a localized aneurysm, delayed acute dissecting aneurysm or intraoperative acute dissecting aneurysm.[15,16] Patients predisposed to this event may have mild dilatation and undue calcification of the ascending aorta, and internal mammary-coronary arterial bypass grafts might be considered when myocardial revascularization is required for these high risk patients.[17] In any event, in our Case 3 it appears that postoperative adhesions prevented rupture into the pericardium with tamponade and permitted the formation of an aorta-right ventricular fistula that allowed time for diagnosis and intervention.

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Location of Myocardial Infarcts: A Confusion of Terms and Definitions

WILLIAM C. ROBERTS, MD, FACC
JULIUS M. GARDIN, MD†

Bethesda, Maryland
Washington, D.C.

Among patients with clinical features suggesting acute myocardial infarction, the standard 12 lead electrocardiogram has been extremely useful during the past 50 years in establishing the diagnosis of myocardial necrosis. In contrast to some previous reports,[1–3] the paper by Sullivan and associates[4] in this issue of the Journal also demonstrates that the electrocardiogram is extremely useful in establishing the diagnosis of healed myocardial infarction. Among their 50 necropsy patients with subendocardial or transmural left ventricular scars, or both, the electrocardiogram showed changes indicative of healed infarction in 47 (94 percent).

Electrocardiogram As Predictor of Infarct Location

Although the electrocardiogram is excellent in detecting the presence of myocardial infarction, many studies have shown that it is not as reliable in pinpointing the exact anatomic location of the myocardial infarct. In the study by Sullivan et al.,[4] for example, the precise electrocardiographic location of the healed myocardial infarct was confirmed at necropsy in only 7 (15 percent) of the 47 patients with an electrocardiographic diagnosis of healed myocardial infarction (Table I). Although the electrocardiogram infrequently predicts the precise location of a myocardial infarct, the study by Sullivan et al.[4] indicates that the electrocardiogram is indeed a good indicator of the general location of a healed myocardial infarct. It is very reliable, for example, in distinguishing between infarcts involving the anterior wall from those involving the posterior wall, but it is unreliable in separating the various subdivisions of anterior and posterior wall infarcts. It is unreliable in sorting out isolated anterior wall infarcts from anterolateral or anteroseptal infarcts or posterolateral from posteroseptal or isolated posterior wall infarcts or in detecting posterior wall infarcts in patients who also have anterior wall infarcts. In addition, it is unreliable in predicting whether an infarct involves the basal or the apical portion of the left ventricle and, as shown by Sullivan et al.,[4] it is a poor predictor of whether a healed infarct is subendocardial or transmural in location.

Although the electrocardiogram is very reliable in predicting the presence of and the general location of a myocardial infarct, it is far less reliable in predicting the extent of an infarct. Among the 47 patients with electrocardiographic evidence of healed myocardial infarction studied by Sullivan et al.,[4] the extent of the fibrosis was accurately predicted by electrocardiogram in only 12 (26 percent); in 33 patients (70 percent), the myocardial infarct was more extensive at necropsy than predicted by electrocardiogram and in only 2 (4 percent) was it less extensive at necropsy than had been predicted by electrocardiogram during life (Table I).

The study by Sullivan et al.[4] reemphasizes the difficulty of making electrocardiographic-morphologic correlative analyses. One problem is the wide range of myocardial lesions in most study populations. Of their 50 patients, 44 (88 percent) had more than one healed myocardial infarct and, indeed, more than half (52 percent) had three or more healed infarcts. In addition, although all 50 patients had a healed myocardial infarct, 10 of them also had acute infarcts that, obviously, also affected the electrocardiographic patterns. Furthermore, nearly one half of their 50 patients (46 percent) had only a subendocardial infarct at necropsy.

Electrocardiographic and Morphologic Terminology

Another problem in these correlative studies is terminology. In the study by Sullivan et al.,[4] the location of the infarct anatomically in the left ventricle was

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland and the Division of Cardiology, Department of Medicine, Georgetown University, Washington, D.C. Manuscript received June 22, 1978; revised manuscript received August 15, 1978, accepted August 15, 1978.

† Present address: Division of Cardiology, Department of Medicine, Northwestern University, Chicago, Illinois.

Address for reprints: William C. Roberts, MD, Building 10A, Room 3E30, National Institutes of Health, Bethesda, Maryland 20014.

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

TABLE I

Location of Healed Myocardial Infarct by Electrocardiogram and at Necropsy. Observations in 47 Necropsy Patients (Data of Sullivan et al.[4])

ECG Location of Healed Myocardial Infarct	Total Patients (no.)	Location of Healed Myocardial Infarct at Necropsy: Patients With ECG Infarct Location Confirmed				Patients With Infarct Location Different From That of ECG			
			Extent of Infarct				Extent of Infarct		
		Total	Same as in ECG	Greater Than in ECG	Smaller Than in ECG	Total	Same as in ECG	Greater Than in ECG	Smaller Than in ECG
Inferior	6	3	1	2	0	3	1	2	0
Inferobasal	1	1	1	0	0	0	0	0	0
Inferior + inferobasal	3	2	0	2	0	1	0	0	1
Anteroseptal	10	10	0	10	0	0	0	0	0
Anterolateral	6	4	0	4	0	2	1	1	0
Anteroseptal + anteroseptal	7	2	2	0	0	5	1	3	1
Inferior + anteroseptal	11	9	3	6	0	2	0	2	0
Inferior + anterolateral	3	1	0	1	0	2	2	0	0
Totals	47	32 (68%)	7	25	0	15 (32%)	5	8	2

ECG = electrocardiogram.

categorized into eight separate groups (anteroseptal, anterolateral, anterobasal, inferior, inferobasal, lateral, septal and apical), but there was overlap among groups. For example, the "anterobasal" and "anterolateral" groups included infarcts with involvement of the ventricular septum as did the "anteroseptal" group. There was no "inferoseptal" group so that the "inferior" group included infarcts with involvement of the ventricular septum. The "inferior" group, however, included only the mid 3 cm portion of the left ventricle if viewed on a longitudinal axis, whereas the "inferobasal" group included only involvement of the basal 2 cm of the left ventricle. Sullivan et al.[4] also used the terms "subendocardial" and "transmural," "extensive" and "limited," "apical segment" and "large segment" to describe the locations and extent of myocardial infarcts. With the exception of the "apical segment" (apical 2 cm), these terms were not defined. Thus, a total of 14 terms were utilized to describe the anatomic locations of one or more myocardial infarcts. Applying 14 terms to 50 patients, 88 percent with multiple healed infarcts and 10 with acute infarcts as well, dilutes the figures considerably for each subgroup of patients. Although Sullivan et al.[4] utilized 14 terms to describe the anatomic locations of myocardial infarcts, only 5 terms (anteroseptal, anterolateral, inferior, inferobasal and apical) were used to describe *electrocardiographic* locations of myocardial infarcts.

To diminish confusion between electrocardiographic and anatomic localization of myocardial infarcts, utilization of a common terminology would appear ideal. Certain terms used in electrocardiographic localization of myocardial infarcts are usually not used to designate their location at necropsy. The terms "inferior," "diaphragmatic" and "true posterior," for example, are primarily electrocardiographic terms and are not ideal because they break the principle of parallelism. Their opposites—namely, "superior," "sternal" or "false posterior" (or indeed "true anterior" or "false anterior")—are never used. Therefore, these terms might best be eliminated so that the same terms may be used both electrocardiographically and anatomically. "Inferior" and "diaphragmatic" myocardial infarcts are simply those involving the "posterior" left ventricular wall, primarily the "posteroapical" portion. "True posterior" generally has been considered "posterobasal," but evidence for this is not firm.

Proposed Terminology for Anatomic Location of Infarct

Because the normal left ventricle at necropsy and in ventricular systole during life is in essence a *cone*, proper description of the location of a myocardial infarct of the left ventricle necessitates designation of the portion or portions of involvement of each of the three dimensions of the cone: (1) the *circle*, (2) the *thickness*, and (3) the *length* (top to bottom) (Fig. 1).

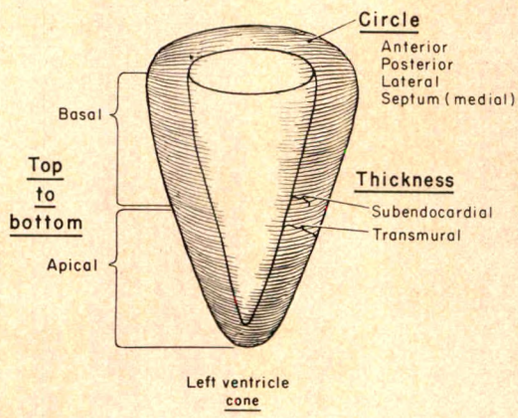


FIGURE 1. Diagram illustrating the three dimensions of the left ventricle as a cone, for localization of infarction.

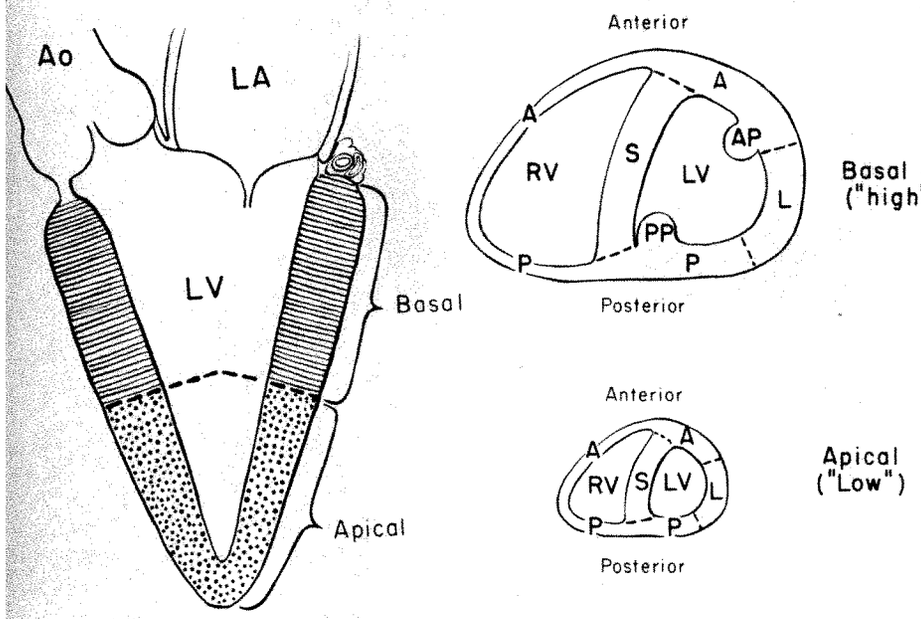


FIGURE 2. Diagrams showing the left ventricle (LV) illustrated as a cone **(left)** and transverse cuts across the right (RV) and left ventricles **(right).** The length of the ventricle is divided into basal and apical halves. The larger transverse slice **(upper right)** is from the basal half and the smaller transverse slice, from the apical half. The **dotted lines** serve to define the various compartments of the left ventricle. A = anterior wall of the left ventricle and anterolateral wall of the right ventricle; Ao = aorta; AP = anterolateral papillary muscle; L = lateral wall of left ventricle; LA = left atrium; P = posterior wall of the right and left ventricles; PP = posteromedial papillary muscle; S = ventricular septum.

The circle includes the *anterior, posterior* and *lateral* ree walls and the *ventricular septum.* The thickness nay be designated as *subendocardial,* defined as the nner half, *subepicardial,* defined as the outer half, and *ransmural,* defined as involvement of both subendo- ardium and subepicardium. We prefer using "suben- locardium" to designate the inner half, rather than the nner third, of the myocardial wall, because most sub- ndocardial infarcts involve only the inner third, and, herefore, by using the half-way cutoff point, a clear lemarcation usually is present between subendocardial nd transmural areas. Furthermore, most transmural nfarcts involve more than 75 percent of the myocardial vall and, consequently, are clearly separable from in- arcts limited to the subendocardium. The length or top o bottom dimension may be divided into basal one- hird, mid one-third and apical one-third or simply into *asal one-half* ("high") and *apical one-half* ("low") Fig. 2). We prefer the latter because there is too much verlap when the ventricles are divided longitudinally nto thirds. The specific compartments of the walls of he cardiac ventricles are shown diagrammatically in 'igure 2. Designating each of the various compartments f the heart is obviously somewhat arbitrary. We in- lude, for example, the anterolateral papillary muscle f the left ventricle in the anterior compartment, al- hough it could as easily be included in the lateral ompartment, or be split in half, in the manner of Sul- ivan et al.,[4] who included half of this structure in their anterobasal" compartment and the other half in their lateral" compartment. The portion of ventricle at each nd of the ventricular septum, when viewed ransversely, could be included in either the posterior r the anterior compartment or in the ventricular sep- um. We prefer to include these junction points between ight and left ventricular free walls as part of the ven- ricular septum. We divide the right ventricular free vall into two compartments (anterolateral and poste- rior) as contrasted to the three free wall compartments of the left ventricle (anterior, posterior and lateral).

To show the portion or portions of the cardiac ventricles involved by myocardial infarcts, the ventricles are divided into basal and apical halves (Fig. 2). Three portions of the *basal* half infrequently are sites of myocardial infarction—namely, the anterior and anteroseptal compartments of the left ventricle and the anterolateral compartment of the right ventricle. "Anterior" myocardial infarction spares the right ventricular free wall, whereas nearly 25 percent of patients with "posterior" left ventricular myocardial infarction have involvement of all or portions of the posterior wall of the right ventricle.[5] Most patients with "posterior" myocardial infarction have involvement of portions of all of the posteromedial papillary muscle of the left ventricle. In contrast, many patients with "anterior" myocardial infarction have no involvement of the anterolateral papillary muscle of the left ventricle.

One problem in designating a myocardial infarct as "anterior" or "posterior" is that each term is usually only partially correct. A large infarct, for example, may be limited to the posterior, posteroseptal or posterolateral portion of left ventricle in its basal half, whereas the area of myocardial involvement may be completely circumferential in much or some of the apical portion of left ventricle. Likewise, an area of myocardial infarction may be entirely subendocardial in one portion and transmural in another.

Correlative Electrocardiographic Patterns

Electrocardiographic patterns for localizing myocardial infarcts in each of the three dimensions of the cone are more often nonspecific than specific. These patterns will be summarized as follows:

Anterior wall of the left ventricle: Myocardial infarction infrequently involves the basal portion of the

anterior wall of the left ventricle. In only 3 of the 50 patients (or in only 3 of 78 separate infarcts) with healed myocardial infarction described by Sullivan et al.[4] was the anterobasal segment of the left ventricle the site of infarction, and each of these patients also had infarction involving other segments of the left ventricle. Thus, electrocardiographic "anterior" myocardial infarction nearly always indicates involvement of all or portions of the apical half of the left ventricle and is characterized, in general, by the presence of Q or QS waves of greater than 0.03 second in lead V_1 or V_2, or both.[6] However, infarcts are infrequently limited to just the anterior wall of the left ventricle. None of the 50 patients of Sullivan et al. had isolated anterior wall infarction. The lateral or septal wall (or both) is usually also involved. An *anteroseptal* infarction is usually characterized by Q or QS waves in lead V_3 or V_4, or both[7,8] and an *anterolateral* infarction, by the presence of Q or QS waves in lead V_5 or V_6, or both, and sometimes in leads I or aVL, or both, in addition to the expected Q or QS waves in leads V_3 or V_4, or both.[9–11]

Posterior wall of left ventricle: Although electrocardiographic differences between "true posterior" ("plain posterior") and "inferior" ("diaphragmatic" or "inferoposterior") myocardial infarction have been described,[11] the evidence is not convincing that "posterior" myocardial infarction involving the basal half of the left ventricle can be distinguished electrocardiographically from "posterior" myocardial infarction involving the apical half of this ventricle. ("True posterior" myocardial infarction has been characterized by "tall" [R to S ratio equal to or greater than 1] and "broad" [duration equal to or greater than 0.04 second] R waves in lead V_1 or V_2, or both; "inferior" infarction, by Q waves with a duration of 0.04 second or more in leads II, III and a VF.) Furthermore, although it has been suggested that the additional presence of Q waves in leads V_5 and V_6 denotes involvement (extension) of the "posterolateral" wall,[9] myocardial infarction involving the "posterolateral" wall cannot be reliably differentiated from myocardial infarction involving the "posteroseptal" wall and neither can be reliably delineated from infarction limited to the "posterior" free wall of the left ventricle.[11–13] Thus, "posterior" myocardial infarction with or without involvement of the adjacent septal or lateral walls generally is characterized by Q or QS waves in leads II, III and a VF or the presence of R waves that are broad (0.04 second or more) and tall (R to S ratio more than 1) in lead V_1 or V_2, or both.

Myocardial infarction involving only the ventricular septum, the lateral wall of the left ventricle, the papillary muscle or the right ventricle: In contrast to its ability to distinguish between myocardial infarction involving the "anterior" wall from that involving the "posterior" wall of left ventricle, the electrocardiogram provides no specific pattern to indicate infarction of the ventricular septum,[8,12] the lateral wall of the left ventricle,[14,15] the papillary muscle or the right ventricle.[5,12] However, myocardial infarction is rarely if ever limited to the lateral wall of the left ventricle or to the ventricular septum or the right ventricle. Thus, whenever the ventricular septum or the left ventricular lateral wall is the site of myocardial infarction, either the anterior or the posterior wall is nearly always involved as well. Moreover, myocardial infarction secondary to coronary arterial narrowing with involvement of the right ventricle is always associated with "posterior" left ventricular infarction, never isolated "anterior" left ventricular infarction.[5] Consequently, the anterolateral wall of the right ventricle is never the site of myocardial infarction unless the entire posterior right ventricular wall is either necrotic or fibrotic, or both. Also, infarction of the posteromedial papillary muscle occurs in most patients with "posterior" infarction; therefore, involvement of this structure can be predicted simply from knowledge that the myocardial infarct is "posterior." In contrast, a high percent of patients with left ventricular "anterior" wall myocardial infarction do not have involvement of the anterolateral papillary muscle; therefore, involvement of this structure cannot be predicted reliably from knowledge that the myocardial infarction involves the "anterior" wall.

Summary

The terminology applicable for describing the location of a myocardial infarct at necropsy is applicable for defining its location by electrocardiogram. Certain terms used primarily electrocardiographically—namely, "inferior," "diaphragmatic" and "true posterior"—should be avoided because their opposites are not used. Ideally, a proper description of the location of a myocardial infarct should include a definition of its involvement in each of the dimensions of the left ventricle (considered as a cone): the portion of the walls of the *circle* involved (anterior, posterior, lateral and septal); the amount of the wall's *thickness* involved (transmural or nontransmural [subendocardial]) and the portions of the wall's *length* involved (basal half or apical half, or both). Certain portions of the walls of both the left and the right ventricles are rare sites of myocardial infarction, and knowledge of these sites helps in more precisely predicting by electrocardiogram the location of the myocardial infarct. Infarction involving the *anterior* wall of the left ventricle rarely is limited to just its basal one-half; therefore, anterior myocardial infarction, for practical purposes, indicates involvement of at least the apical half of this ventricle. In contrast, myocardial infarction involving the basal half of the *posterior* left ventricular wall is common, but the electrocardiogram is not accurate in differentiating posterobasal from posteroapical infarction. Furthermore, the electrocardiogram provides no specific pattern to indicate myocardial infarction of the ventricular septum, the lateral wall of left ventricle, either the posterior or the anterolateral wall of the right ventricle or the papillary muscle. Infarction of the right ventricle virtually never occurs with isolated "anterior" myocardial infarction of the left ventricle. In contrast, nearly 25 percent of patients with "posterior" transmural myocardial infarction also have associated infarction involving at least the posterior wall of the right ventricle.

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LETTERS TO THE EDITOR

CARDIAC CATHETERIZATION AND INTRAAORTIC BALLOON COUNTERPULSATION

Intraaortic balloon counterpulsation is known to be effective in patients with severe heart failure from myocardial infarction. Hagemeijer et al.[1] have elegantly reported on a series of 25 patients so treated. Each instance represented the concerted efforts of cardiologist and surgeon. These results certainly justify further consideration of balloon pumping in these critically ill patients. However, an equally impressive aspect of this study is that none of the five patients dying during balloon pumping were studied with cardiac catheterization, and of the six patients surviving less than 3 months, only one was studied. Eight cardiac catheterizations were performed in the full series of 25 patients.

Controversy continues as to the merit of early cardiac catheterization after myocardial infarction. However, an entirely different class of patients is examined here, because each had cardiogenic shock to a degree that would be acknowledged by most observers. Placement and management of an intraaortic balloon is a more hazardous undertaking than the conduction of a catheterization by an experienced cardiologist using adequate facilities. I believe that almost every patient treated with balloon counterpulsation for cardiogenic shock should be studied after his condition has stabilized and certainly while the balloon is still in place. Frequently, the surgeon is granted only one trouble-free passage of this device through diseased vessels, and the situation of having to replace a balloon subsequently for catheterization and possible surgery in a patient whose condition is deteriorating is to be avoided if at all possible. Our cardiologists using the groin approach have not experienced major difficulty in studying "around" the balloon, and this technique is well described by others.[2] Indeed, they have appreciated the support offered by the device, and in most cases have been permitted their full series of injections on these critically ill patients.

Left ventricular aneurysm, left main coronary stenosis with infarction related to right-sided lesions and papillary muscle rupture are conditions that could well arise in any series of this size, and patients with these findings should be considered for early operation. Use of the balloon during catheterization, continuation through anesthetic induction and onto cardiopulmonary bypass affords continuous support of these patients during the periods of greatest peril.

I enjoyed this paper, which shows the benefit of intraaortic balloon counterpulsation support in cardiogenic shock, and would only add that cardiac catheterization be undertaken early in the period of stabilization after balloon pump placement, when options for surgical management may still be reasonable.

Cordell H. Bahn, MD, FACC
Tacoma, Washington

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REPLY

Now, in 1978, we fully agree that almost every patient treated with balloon counterpulsation for cardiogenic shock should undergo diagnostic catheterization after his condition has stabilized, with the balloon still in place. As the dates listed in Table II of our paper show, it took us quite some time to get used to the concept of intraaortic balloon pumping without surgery. Catheterization was not considered unless cardiac surgery seemed likely to correct the mechanical cause of cardiogenic shock (rupture of a papillary muscle or of the interventricular septum[1]). Catheterization is now carried out to document the extent of the lesions as soon as the patient's condition stabilizes on circulatory assistance. These studies are conducted whether or not the patient is being considered for surgery.

TABLE I

Cardiac Catheterization Data on Patients With Cardiogenic Shock

CAD	Died During IABP	Survival <1 year	Survival >1 Year
LAD	1	2	2
LCx	1	0	1
RCA	0	0	1
LAD + LCx	0	1	1
LAD + RCA	0	0	1
LCx + RCA	0	0	0
LAD + LCx + RCA	2	4	3
Total	4	7	9

CAD = coronary artery disease; IABP = intraaortic balloon pumping; LAD, LCx and RCA = left anterior descending, left circumflex and right coronary artery, respectively.

H. R. Michels, MD and P. W. Serruys, MD recently reviewed all our catheterization data on patients with cardiogenic shock up to January 15, 1978. Twenty patients have now been catheterized during circulatory assistance without any untoward effect, even during angiography (Table I). Column 3 lists patients treated less than 1 year ago; all of them are alive. No patient in this series underwent cardiac surgery. Lest the dates of Table I be misunderstood, these deal only with patients who were catheterized; the condition of several patients with shock did not improve and they died before stabilization and before catheterization could be carried out.

The likelihood of survival for patients with cardiogenic shock after an acute myocardial infarction is still 50 percent when therapy consists of intraaortic balloon pumping without surgery.[2] However, it should not be forgotten that these patients are extremely fragile: Medical management of patients with shock undergoing prolonged intraaortic balloon pumping remains extremely delicate.[3]

Frans Hagemeijer, MD, FACC
John D. Laird, D Phil
Max M. P. Haalebos, MD
Paul G. Hugenholtz, MD, FACC
Thoraxcenter
Erasmus University
Rotterdam
The Netherlands

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INTERNAL SYSTOLIC TIME INTERVALS IN HYPERTROPHIC CARDIOMYOPATHY

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Stefadouros et al.[1] report a close correlation between internally measured preejection period/ejection time(PEP/LVET) ratio and peak and mean left ventricular outflow tract pressure gradient in patients with hypertrophic cardiomyopathy. We have collected similar data in 15 subjects with hypertrophic cardiomyopathy and 5 normal subjects studied at rest and during isoproterenol stimulation with high fidelity pressure transducers as previously described by us.[2] Our findings and conclusions differ from those of Stefadouros et al.

Eight of our patients (group 2) had a left ventricular outflow tract gradient at rest that was in five augmented by supine exercise. In seven patients (group 3) a gradient developed only with provocation. Finally, five normal patients (group 1) undergoing cardiac catheterization for chest pain were studied at rest and during exercise and isoproterenol infusion and were utilized as a control group. Our findings are presented in Table and Figure 1.

In contrast to the data of Stefadouros et al., the correlation between PEP/LVET ratio and left ventricular outflow tract gradient in our subjects was not significant. In our five normal subjects (group 1), the PEP/LVET ratio was significantly reduced by isoproterenol infusion in a manner similar to that described by Stefadouros et al. in their patients with hypertrophic cardiomyopathy. Also, we found in our patients with cardiomyopathy (group 2) no correlation between the left ventricular outflow tract gradient at rest and the simultaneous high fidelity internally measured PEP/LVET ratio. Among our seven patients whose outflow tract gradient was present only during isoproterenol stimulation (group 3), resting PEP/LVET ratios were widely scattered (range 0.273 to 0.423) in contrast to four patients of Stefadouros et al. with no resting gradient whose ratios were tightly clustered (0.423 to 0.452).

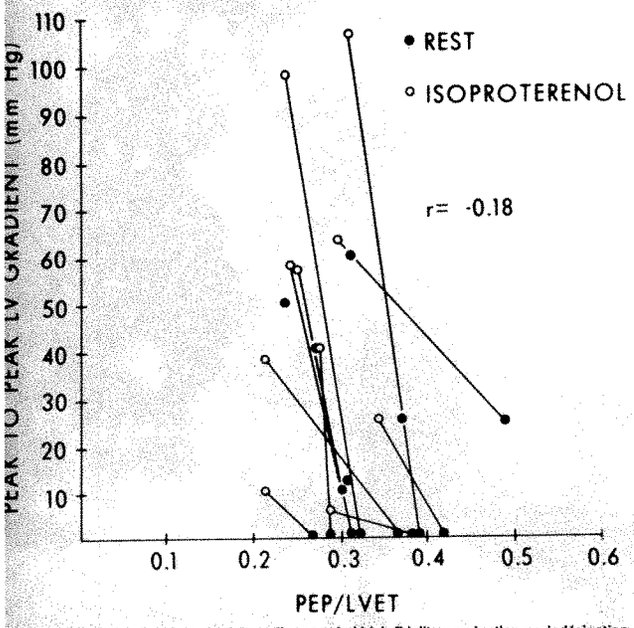


FIGURE 1. Relation between the internally recorded high fidelity preejection period/ejection time (PEP/LVET) ratio and the peak to peak left ventricular (LV) outflow pressure gradient at rest and during isoproterenol infusion.

TABLE I

Internal Preejection Period/Ejection Time (PEP/LVET) Ratio in Various States

Group	Subjects (no.)	Rest	Isoproterenol	Exercise
1	5	0.351 ±0.016	0.307 ±0.017†	0.036 ±0.018†
2	8	0.332 ±0.080	—	0.316 ±0.05
3	7	0.347 ±0.05	0.317 ±0.04	0.270 ±0.05*

* P (probability) <0.01; † P <0.05. (The only significant P values indicated an intragroup difference between the resting state and the forms of intervention. There were no significant intergroup differences.)

Finally, there was no significant difference in PEP/LVET among our three groups either at rest or during exercise or isoproterenol infusion (Table I), as defined by Student's t test. We therefore disagree with the conclusion of Stefadouros et al. that PEP/LVET ratios at rest or during isoproterenol stimulation are accurate indexes of outflow tract gradients in hypertrophic cardiomyopathy.

Gregory S. Uhl, MAJ, USAF, MC
Joseph P. Murgo, LTC, MC, FACC
John R. Logsdon, MAJ, MC
Barry R. Alter, MAJ, MC
James F. Dorethy, MAJ, MC
Cardiology Service
Department of Medicine
Brooke Army Medical Center
Fort Sam Houston, Texas

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REPLY

Uhl and his associates point out that their results do not agree with our finding of a close correlation between preejection period/ejection time (PEP/LVET) ratio and the peak left ventricular outflow pressure gradient. We assume that their expression "similar data" implies measurement of systolic time intervals and simultaneous peak left ventricular outflow gradient in the manner used in our analysis of left ventricular and aortic pressure signals. The reason for the disagreement in the results of the two studies is not obvious, but may be related to differences in patient selection. Thus, we specifically excluded from our study patients with major arrhythmias, atrioventricular or intraventricular conduction defects, other congenital or acquired cardiac lesions (except for mild mitral or aortic regurgitation) and left ventricular dysfunction as evidenced by an angiographic left ventricular ejection fraction of less than 0.50. We do not know whether these criteria for exclusion were applied in the study of the Uhl et al. In our study all patients had a significant (more than 30 mm Hg) resting or provocable left ventricular outflow gradient in addition to the angiographic criteria of the disease. In the study of Uhl et al. three of eight patients of group 2 with a resting gradient of less than 30 mm Hg were not subjected to isoproterenol stimulation, and in three of seven patients in group 3 the left ventricular outflow gradient, being zero at rest, failed to reach 30 mm Hg during isoproterenol stimulation.

(Incidentally, there is a small, inconsequential error in Figure 1 of Uhl et al.: It shows seven patients with and eight patients without a resting left ventricular pressure gradient, instead of eight and seven patients, respectively, as mentioned in their text and Table I). In our study, the relation between peak left ventricular outflow gradient and the PEP/LVET ratio (shown in our Figure 4) was based on a much larger number of data points (183), because most patients contributed several points as a result of spontaneous variation in the gradient during cardiac catheterization. We do not know whether this phenomenon was present in the patients of Uhl et al. and, if so, the criteria used to select one data point from each patient at rest. As can be seen from Figure 4 of our paper, the inclusion of postpremature beats expanded the domain of peak left ventricular pressure gradient to more than twice that observed in the patients of Uhl et al. in whom such beats were presumably not included.

We believe that these differences may be responsible for the apparent discrepancy in the findings and the conclusions of the two studies. Finally, our paper did not state that the PEP/LVET ratios at rest or during isoproterenol stimulation are "*accurate* indexes" (our italics) of the outflow tract gradients. We did state our belief that the systolic time intervals "... may be useful in the noninvasive assessment of outflow obstruction in this disease."

Miltiadis A. Stefadouros, MD
Martin J. Frank, MD
Medical College of Georgia
Augusta, Georgia

PACEMAKER TREATMENT OF DRUG-RESISTANT ATRIAL TACHYCARDIA

In a recent article[1] we described use of a specially designed implantable pacemaker for coupled atrial stimulation in an adolescent boy with severe congestive heart failure associated with repetitive drug-resistant tachycardia. We now have further data on this patient:

On December 15, 1977, 4 years and 9 months after the initial pacemaker implantation, the patient was asymptomatic and his physical activities were unrestricted. The physical examination and a chest roentgenogram were normal except for the presence of the pacemaker. The 12 lead electrocardiogram and a 24 hour Holter monitor showed a normal contour during sinus or pacemaker escape rhythm. A treadmill exercise test was normal. The second pulse generator showed signs of battery depletion 25 months after implantation and was removed on December 28, 1977. During surgery, the diastolic cathodal threshold of the atrial pacing lead was 0.5 milliamperes, similar to the acute threshold obtained during implantation. The P wave amplitude recorded from the atrial sensing lead was 2.5 mv. The atrial leads were left in situ with the proximal ends capped. A new pulse generator was not implanted because we believe that the patient no longer needs pacemaker support.

Emanuel R. Arbel, MD
Cardiovascular Institute
Michael Reese Hospital and
Medical Center
Chicago, Illinois

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ECHOCARDIOGRAPHIC ESTIMATION OF PEAK LEFT VENTRICULAR PRESSURE IN AORTIC STENOSIS

Aziz et al.[1] confirm the close relation between echocardiographic end-systolic ventricular dimensions and left ventricular pressure in children with aortic stenosis that I and my co-authors first demonstrated in 1975,[2] but they show an even closer correlation between ventricular pressure and end-diastolic dimensions. The results of a larger personal study[3] of 95 patients, mainly adults, differ from those of Aziz et al. in that peak left ventricular pressure correlated more closely with end-systolic dimensions ($r = 0.91$) than with end-diastolic dimensions ($r = 0.79$). In fact, their correlation using end-diastolic dimensions ($r = 0.92$) is no better than that demonstrated by others[4,5] using end-systolic dimensions, and it relies on a "fudge factor" by taking the mean of posterior and septal wall thicknesses.

Aziz et al. show that peak systolic wall stress varies little in patients with compensated pressure overload, and they correctly point out that end-diastolic dimensions are more appropriate when considering peak systolic wall stress. However, end-systolic wall stress also remains constant in pressure overload,[6] thus supporting the use of end-systolic dimensions. Although the findings of Aziz et al. on systolic wall stress are interesting, I cannot agree with their suggestion that when estimating peak left ventricular pressure with echocardiography end-diastolic dimensions should be used; I favor the method using end-systolic dimensions, which continues to provide useful estimates of the severity of aortic stenosis.

David Bennett, MD, MRCP
Cardiac Department
The Radcliffe Infirmary
Oxford, England

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REPLY

The model we used for the relation between echocardiographic left ventricular wall and cavity dimensions and peak systolic left ventricular pressure utilizes the end-diastolic h/r ratio; it is based on Laplace's formulation for wall stress and has a sound theoretical basis. If one chooses to use end-systolic dimensions, then the stress relates to the end-systolic left ventricular pressure and not the peak systolic pressure, which occurs early in systole before any significant wall thickening. Bennett et al. have used peak systolic left ventricular pressure while using the end-systolic chamber dimensions; measurements that occur at completely different times in the cardiac cycle. Thus, the estimated "c" or the conversion "factor" is not in principle a measure of left ventricular stress at end-systole. For this reason, in our opinion, the basic assumptions of Bennett et al. are invalid and we would not favor a method employing end-systolic dimensions unless appropriate regression statistics on suitable populations prove these more useful for pressure estimations.

Blackwood et al.,[1] in a recent publication concerning pressure estimates in children with aortic stenosis derived from left ventricular echocardiograms, have modified with "c" to a figure of 245 from the originally derived value of 225 in normal adults. We used the mean of end-diastolic left ventricular septal and posterior wall dimensions ($\bar{h}$) (which Bennett inadvisedly calls a "fudge factor") because in our study the left ventricular mass (estimated using both these dimensions rather than posterior wall only) to left ventricular end-diastolic volume ratio showed a greater correlation with left ventricular pressure, a result that is in agreement with those of others.[2] Because the left ventricular wall thickness is not necessarily uniform throughout its circumference, in normal or hypertrophied hearts, measurements at more than one area may be more representative of a more appropriate wall dimension. Finally, additional observations by us in 18 children with subaortic stenosis have confirmed our published observations regarding the usefulness of the end-diastolic $\bar{h}/r$ ratio for evaluating the peak left ventricular pressure.

Kalim U. Aziz, MD
Albertus van Grondelle, MS
Milton H. Paul, MD, FACC
Alexander J. Muster, MD, FACC
Division of Cardiology
Willis J. Potts Children's Heart Center
The Children's Memorial Hospital

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ECHOCARDIOGRAPHIC PATTERNS OF PROSTHETIC VALVE MALFUNCTION

Bernal-Ramirez et al.[1] describe two echocardiographic patterns of a malfunctioning Björk-Shiley mitral valve prosthesis: (1) a rounded upstroke and downstroke pattern of opening and closing that they found in two cases of thrombosis, and (2) an unusual "hump" during the opening phase that they believe correlates with paravalve leak.

We agree that thrombosis on the prosthesis may result in a rounded upstroke and downstroke pattern; we recorded this feature[2] as well as a prolonged interval between aortic closure and mitral valve opening in a patient whose Smeloff-Cutter mitral prosthesis was found to have a big clot at surgery. As for the early diastolic hump they brilliantly describe, we have two comments:

1. We recorded the same pattern (Fig. 1) in a patient with a Beall mitral valve prosthesis found to have severe disc variance at autopsy. We therefore do not agree that this pattern is a typical diagnostic sign of valve detachment.

2. We also think that the slow backward and forward movement cannot be attributed to the disc (which has a fixed excursion) but only to the anterior movement of the anulus pushing forward the whole valve. This exaggerated movement of the anulus can be clearly detected in the echocardiograms presented by the authors and mimics exactly the so-called "hump" of the disc.

Gaja Jacovella, MD
Paolo Giampaolo, MD
Giancarlo Gambelli, MD
Ospedale S. Camillo
Dipartimento di Cardiologia
Rome, Italy

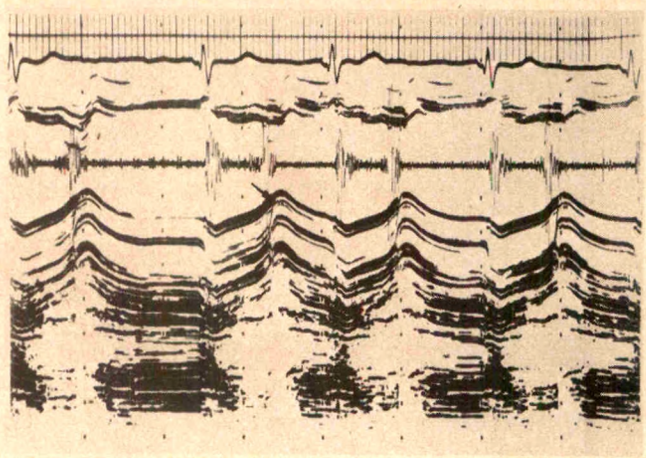


FIGURE 1. Early diastolic "hump" **(arrow)** in a case of severe disc variance.

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REPLY

The points raised by Jacovella et al. may well be correct. The diastolic "hump" probably means the valve is insufficient and, with the type of valves we discussed, the most common cause for this abnormality would be valve detachment. Additional experience suggests that the primary motion abnormality in this regard does rest with the anulus.

John H. Phillips, MD
Cardiology Section
Department of Medicine
Tulane Medical Center
New Orleans, Louisiana

OPTIMAL ELECTROCARDIOGRAPHY

One of the good things about taking a stand is that it provides a useful starting point for further discussion. This being so, readers of the 10th Bethesda Conference report[1] now have the responsibility of voicing any disagreements they may have with the recommendations put forward.

1. Terminology: With respect to the recommendations regarding terminology made by Task Force I, I take issue with their employment of the terms describing the age of an infarction. They recommend that *acute* should mean less than 3 days, *recent* less than 1 month, and *old* more than 3 months. Apart from leaving a hiatus in which infarcts older than 1 month yet younger than 3 months are not described, there are other problems with these terms. The Task Force's arbitrarily strict 3 day rule regarding the use of *recent* requires an accuracy of timing that is beyond the scope of clinical electrocardiographic interpretation, except in the rare instance where an immediately pre-infarct tracing is available. According to the Oxford English Dictionary, recent means "fresh; not yet affected by decay, decomposition, or loss of moisture." There is nothing in this definition to exclude the immediate past. The term *acute* is more applicable to a clinical condition

"coming sharply to a point or crisis in severity" than to an electrocardiographic pattern that may be associated with an asymptomatic event. Clearly the interpreter cannot say whether the infarction occurred acutely, only that it occurred recently. Furthermore, the use of *acute* as a descriptive implies the existence of a *chronic* alternative, yet chronic infarction is a term of obscure meaning that is seldom used. The Task Force's dissatisfaction with the term *evolving,* and similar terms, does not take into account the usefulness of characterizing the pattern seen when the infarction is no longer recent but has not yet stabilized or evolved into the fixed pattern of an old infarction. The more commonly used term *serial changes* (which they do not mention) says the same thing but it allows the possibility of conflicting logic, as in "serial changes (of anterior infarction) but no significant change since previous tracing."

2. Record storage: The comments of Task Force II under the heading "Magnetic Storage of Electrocardiographic Records" seem to invite my comment because I am a co-author of the sole reference cited for compression schemes, mentioned in the first two sentences of this section. The statement that these schemes "must be extensively verified by independent institutions or organizations before they are accepted" and that they "can result in unacceptable distortion of the primary electrocardiographic waveform" must leave the reader, unfamiliar with our work, with the impression that our compression technique may distort the electrocardiogram. This is incorrect. While it is true that some compression schemes, intended for arrhythmia analysis, may result in distortion, we have made it clear that our compression method—which merely throws away consecutive samplings when there is no change in them and, by keeping a record of the eliminated samples, provides the information necessary for the data to be restored to their original form—produces tracings that are indistinguishable from the original, as our published examples show.[2–4] Indeed, because we have taken considerable pains to obtain data of higher quality than is employed in other computerized electrocardiographic systems, we should hardly find acceptable a compression technique that distorted these data.

3. Derived electrocardiogram: In the same paragraph, relative to their remarks about "the reconstruction of the 12 lead electrocardiogram from the vectorcardiogram" being "probably not valid because coefficients for reconstruction are unique for each individual," it is a pity that Task Force II cited only a single reference, especially since that dealt with reconstructing the vectorcardiogram from the electrocardiogram, rather than vice versa, using only three leads at a time! We have been deriving 12 lead electrocardiograms from the Frank X,Y,Z signals for several years.[5–7] The derived electrocardiograms really do provide an acceptable basis for comparison with the conventionally obtained electrocardiogram.[3] They are so used routinely, though not exclusively, at the Vancouver General Hospital, where they are read by a panel of 12 cardiologists. The best evidence in favor of the remarkable *clinical* equivalence between the two types of tracings is provided by a consecutive series of 150 examples comparing both. Xerox copies of these could be made for the members of the Task Force or other interested groups. Although optimal coefficients should be tailored for each individual, as was done for the National Aeronautics and Space Administration,[8] sufficiently good values can be generalized and yet provide adequate practical performance. The reason for this is that the standard electrocardiogram does not have very good reproducibility; the reproducibility of the derived electrocardiogram is better.

4. Sampling note: Task Force II in the section "Computer Communications and Electrocardiographic Transmission" indicates that a sampling rate of 250 hertz is acceptable. This gives only a 4 msec resolution. Our analog data has a band width of 330 hertz, and we sample them at 1,000 hertz. The following is a set of QRS duration measurements, from a child, made on a series of beats as part of a typical output from our measurement program: 73, 70, 72, 72, 70, 71, 71, 71 msec. Note that the range of beat to beat variation is only 3 msec. This suggests that a 4 msec resolution is suboptimal.

5. Analog versus digital mode: With respect to Table VI, it is a pity that the Task Force did not make it clear that these standards were applicable only to electrocardiographic transmission in analog form. It was the severe limitations of this type of transmission that led us to adopt a digital mode.[3,4]

6. Direct-writing electrocardiographs: Several comments could be made with respect to Table V, which lists the Food and Drug Association and American Heart Association requirements for direct-writing electrocardiographs. However, this does not seem an appropriate place for going into such detail although there are grounds for concern that, by setting standards that instruct how something should be done rather than state what is required, options for future improvements in design may be unnecessarily restricted.

Gordon E. Dower, MB, FACC
Woodward Polar-ECG Service
Vancouver General Hospital
Vancouver, British Columbia
Canada

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NEW MEMBERS

he following individuals were elected to iembership in the American College of Carology on September 20, 1978 in the category idicated.

ELLOWSHIP

BRAHAM, Abraham K., MD, India
DEFUIN, Zosimo A., MD, Bridgeport, CT
DKISON, Harold W., MD, Sante Fe, NM
KHTAR, Syed H., MD, Wausau, WI
KMAN, David, MD, New Orleans, LA
LAVIZADEH, Seyed M., MD, Iran
LDAY, Luis Eduardo, MD, Argentina
LTSCHULLER, Alexander, MD, North Dartmouth, MA
MBROSE, John, MD, New York, NY
NDRIAS, C. Wallace, MD, New London, CT
NGELL, William W., MD, San Jose, CA
PPLEFELD, Mark M., MD, Baltimore, MD
RBEL, Emanuel R., MD, Chicago, IL
RNOLD, Richard S., MD, Daytona Beach, FL
AILS, Richard P., MD, Berkeley, CA
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ASHORE, Thomas M., MD, Durham, NC
AUCUM, Ralph W., Jr., MD, Shreveport, LA
AYLEN, Barry G., MD, Torrance, CA
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OMMER, William J., MD, Sacramento, CA
RENNER, Joel I., MD, Baltimore, MD
ULCHANDANI, Kamlesh V., MBBS, Kankakee, IL
ULLINGTON, Robert H., MD, Phoenix, AZ
USH, Everett M., MD, Toledo, OH
ABEEN, William R., Jr., MD, Los Angeles, CA
HAN, Antonio Q., MD, Oakbrook Terrace, IL
HANT, G. Noel, MD, Canada
HUDASAMA, Lalji S., MB, ChB, Clark, NJ
HUNG, Timothy Kam-Hung, MBBS, Rugby, CA
IAFONE, Russell A., MD, Hartford, CT
LARK, Ralph D., MD, San Francisco, CA
OHEN, Eric D., MD, Albany, NY
OMERFORD, Thomas J., MD, Cleveland, OH
YWINSKI, Jozef K., PhD, Boston, MA
AVIS, Lee Roy, MD, Columbus, OH
EANO, Danilo A., MD, Chicago, IL
E FELICE, Charles E., MD, Baltimore, MD
ORETHY, James F., MD, Sun City, AZ
RASKOCZY, Steven P., MD, Altoona, PA
DUCCI, Hector H., MD, Falls Church, VA
DY, Bun Yok O., MD, Philippines
ECKSTEIN, Paul F., MD, Tampa, FL
ESPER, Ricardo J., MD, Argentina
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FARSHIDI, Ardeshir, MD, Farmington, CT
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FERNANDEZ, Jose J., MD, Tucson, AZ
FIELD, John M., MD, Hershey, PA
FISHBEIN, Michael C., MD, Los Angeles, CA
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FRAZIER, Bruce L., MD, Bakersfield, CA
GAETA, Joseph R., MD, Providence, RI
GAKUBA, Chrysologue, MD, Pikesville, MD
GALBRAITH, Jo Etta S., MD, Little Rock, AR
GARCIA, Jorge M., MD, Washington, DC
GAUGHAN, Gerard L., MD, Boston, MA
GERSH, Bernard J., MB, ChB, Rochester, MN
GIARDINA, Elsa-Grace V., MD, New York, NY
GOLDMAN, Mark R., MD, Boston, MA
GOLDMAN, Steven, MD, Tucson, AZ
GOTTLICH, Charles M., MD, Dallas, TX
GOVINDARAJAN, Rajagopalan, MBBS, Los Angeles, CA
GREENBERG, Barry H., MD, Portland, OR
GREENFIELD, Douglas H., MD, Brooklyn, NY
GREENFIELD, Robert S., MD, Orange, CA
GUNNING, John F., MD, Australia
GUPTA, Madan Lal, MD, Galesburg, IL
HALL, Ronald R., MD, Travis AFB, CA
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HONIG, Howard S., MD, Hanover, NH
HORGAN, John H. S., MB, BCh, Ireland
HORTON, Jack D., MD, Washington, DC
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HUSSAIN, Ahmed T., MBBS, India
HUSSAMI, Sami, MD, Lebanon
INGHAM, Robert E., MD, Walnut Creek, CA
IRVIN, Robert G., MD, Charleston, SC
ISNER, Jeffrey M., MD, Bethesda, MD
JELVEH, Mansoor, MD, New York, NY
JENNINGS, Rufus B., Jr., MD, Norfolk, VA
JOHNSON, Ben D., MD, Little Rock, AR
KARLSBERG, Ronald P., MD, St. Louis, MO
KARRAS, Thomas J., MD, Madison, WI
KENT, Kenneth M., MD, PhD, Bethesda, MD
KHAN, Mushtaq A., MBBS, Chicago, IL
KHAWAJA, Abbas Ali, MBBS, Aurora, IL
KHER, Harkrishan L., MD, India
KHULLAR, Subhash C., MD, Toledo, OH
KHURSEED, Mohammed, MD, Norwalk, CA
KLEIN, George J., MD, Durham, NC
KLUGHAUPT, Martin, MD, Mountain View, CA
KRISLE, George M., III, MD, Knoxville, TN
KULLER, Lewis H., MD, Pittsburgh, PA
KUO, Chien-Suu, MD, Lexington, KY
LAKE, Carol L., MD, Charlottsville, VA
LAO, Edward E. H., MD, Parma, OH
LEE, Danilo G., MD, Oxon Hill, MD
LEE, Won-Kyu, MD, Newark, NJ
LEE, Won Ro, MD, PhD, Washington, DC
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LEVINE, Paul A., MD, Boston, MA
LEVY, James A., MD, Port Chester, NY
LEVY, Meldon C., MD, Los Angeles, CA
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LOMINACK, Edward K., Jr., MD, Greenville, SC
LUEPKER, Russell V., MD, Minneapolis, MN
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MADRAZO, Armando C., MD, Southfield, MI
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MATHEWS, Emmet C., Jr., MD, Richmond, VA
McEWAN, Mary M. Patricia, MD, Canada
MENAPACE, Francis J., Jr., MD, Danville, PA
MENDELSON, Sander H., MD, Washington, DC
MENDIZABAL, Rolando C., MD, Miami Beach, FL
MESSERLI, Franz H., MD, New Orleans, LA
MICHAELSON, Stephen P., MD, Darien, CT
MILLER, Ronald H., MD, Bethesda, MD
MONTEVERDE, John P., MD, Skokie, IL
MORRIS, Andrew L., MD, Canada
MOTRO, Michael, MD, Lido Beach, NY
MURPHY, Thomas E., MD, Evanston, IL
NAFFAH, Paul, MD, Elmwood Park, IL
NEFF, Edward M., MD, Coral Gables, FL
NEWMAN, Benjamin E., MD, Philadelphia, PA
NITITHAM, Karoon, MD, Evanston, IL

NIVATPUMIN, Thasana, MD, Bronx, NY
NODY, Agatha C., MD, New York, NY
O'GRADY, Gerald P., Jr., MD, Santa Cruz, CA
OLDENBURG, Frederick A., MD, Cleveland, OH
OLSON, Robert Wayne, DO, Portland, OR
PARNES, William D., MD, Columbia, MD
PASTORE, John O., MD, Boston, MA
PATEL, Ramesh N., MBBS, Chicago, IL
PESCHIERA, Antonio W., MD, Kalamazoo, MI
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RAHIM, Abdur, MBBS, Miami Beach, FL
RAINWATER, Joseph O., MD, Denver, CO
REEVES, William C., MD, Hershey, PA
RIFKIN, Robert Daniel, MD, Boston, MA
ROBLES De Medina, Etienne O., MD, PhD, Netherlands
ROGERS, Jeffrey P., MD, Grand Rapids, MI
RUBIN, Robert, MD, Hewlett Bay Park, NY
RYAN, J. M. Colman, MB, BCh, San Francisco, CA
SAGAR, Kiran B., MD, Richmond, VA
SAHAB, Joseph G., MD, Leesburg, FL
SALCEDO, Ernesto E., MD, Cleveland, OH
SALIMI, Mostafa, MD, Clifton, NJ
SALLAM, Ismail A., MB, ChB, Kuwait
SANMARCO, Miguel E., MD, Downey, CA
SBARBARO, James A., MD, Burlington, VT
SCHLESINGER, Zwi, MD, Israel
SCHOENBERGER, James A., MD, Chicago, IL
SHAH, Vinaychandra K., MBBS, Leonardtown, MD
SHAVER, Philip J., III, MD, Rancho Mirage, CA
SHEIKH, Mazhar U. H., MBBS, Washington, DC
SHIMOSATO, Shiro, MD, PhD, Martinez, CA
SHULMAN, Joel S., MD, Ft. Lauderdale, FL
SILVERSTEIN, Burton V., MD, Durham, NC
SKLAROFF, Herschel J., MD, New York, NY
SMITH, James W., MD, Boise, ID
SOLOVAY, Mark L., MD, Yuma, AZ
SOYBEL, William M., MD, Waltham, MA
STARK, Jaroslav, MD, England
STONE, Ira M., MD, Ocala, FL
STORCH, Henry D., MD, Jacksonville, FL
STRONG, Michael D., MD, Philadelphia, PA
STRUNK, Brian L., MD, San Francisco, CA
SULLIVAN, Gregory F., MD, Rutherford, NJ
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TABRAH, Farouk A. J., MD, Kettering, OH
TAW, Richard L., Jr., MD, Santa Monica, CA
TEMKIN, Lawrence P., MD, Tucson, AZ
TEW, Franklin T., MD, Orlando, FL
THOMPSON, Stanley I., MD, San Diego, CA
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UY, Santos A., Jr., MD, Cleveland, OH
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VERGARA, George L., MD, Coral Gables, FL
VIGNOLA, Paul A., MD, Boston, MA
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WEINSCHELBAUM, Ernesto E., MD, Argentina
WEIR, Edward K., MD, Minneapolis, MN
WERNER, Jeffrey A., MD, Seattle, WA
WILLIAMS, C. Basil, MD, Ogden, UT
YU, John J. S., MD, Costa Mesa, CA
ZIMMERMAN, Ariaen N. E., MD, PhD, Netherlands

ADVANCE TO FELLOWSHIP

ADAM, Mahmoud H., MD, Cleveland, OH
AL-HANNA, Youssef A., MD, Hartford, CT
ALPERN, Harvey L., MD, Los Angeles, CA
ASOKAN, Sankaran K., MBBS, Paterson, NJ
ASTONE, Robert A., MD, Torrance, CA
AYERDI, Evalt, MD, El Paso, TX
BECKWITH, George H., MD, Pollocksville, NC
BEHARI, Vijay B., MB, BS, Warren, OH
BODE, Robert F., Jr., DO, El Paso, TX
BULLON, Fernando Sarnago, MD, Spain
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HERNANDEZ-LOPEZ, Edgardo, MD, San Juan, PR
HEUPLER, Frederick A., Jr., MD, Cleveland, OH
HILL, Philip E., MD, Petoskey, MI
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JOFFE, C. David, MD, Dayton, OH
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KATZ, Stuart S., MD, Atlanta, GA
KAUFMAN, Joseph A., MD, Las Vegas, NV
KAZANTZIS, Andreas E., MD, Cyprus
KEIVAN, Hossein, MD, Blue Island, IL
KLEINER, John P., MD, Colorado Springs, CO
KLONARIS, John N., MD, Dunedin, FL
KOCH, Francis H., MD, Palo Alto, CA
KOPPES, Gerald M., MD, San Antonio, TX
KOSOWSKY, Bernard D., MD, Boston, MA
KRAUS, Martin E., MD, Phoenix, AZ
KREPS, Edward M., MD, New York, NY
KUMAR, Tumkur B. N., MBBS, Pawtucket, RI
LEE, St. George Tucker, Jr., MD, Charlottesville, VA
LONGO, Michael R., Jr., MD, Sioux Falls, SD
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MAGNIER, Eugene A. H., MD, PhD, Honolulu, HI
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MAYRON, Bart R., MD, Chicago, IL
McGREW, Frank A., III, MD, Memphis, TN
McGUIRE, Michael R., MD, Shawnee Mission, KS
MEHTA, Jawahar L., MBBS, Gainesville, FL
MILLMAN, William L., MD, Oak Park, IL
MIMBS, James W., MD, St. Louis, MO
NAIR, M. R. Sasidharan, MBBS, Southfield, MI
NEWTON, Maury C., Jr., MD, Marietta, GA
OHANESSIAN, Simon, MD, Chardon, OH
PANDIAN, M. Ganesa, MD, India
PATEL, Jayantkumar N., MD, Woodridge, NJ
PAYNE, Robert M., MD, Scottsdale, AZ
PICHARD, Augusto, MD, Scarsdale, NY
PIDOUX, Rene E., MD, Glendale, CA
RANA, Thakor C., MB, BS, Bronx, NY
REAGAN, Patrick J., MD, Auburn, WA
REDUTO, Lawrence A., MD, Houston, TX
ROMEO, Joseph A., MD, Bethesda, MD
ROSENBERG, Donald G., MD, North Miami Beach, FL
ROSENBLATT, Andrew, MD, San Francisco, CA
ROY, Gita, MBBS, Middletown, CT
RUSSO, William L., MD, Memphis, TN
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KANADE, Ashok, MB, BS, New Orleans, LA
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LIEF, Laurence H., MD, La Jolla, CA
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MAHAPATRA, Rajat K., MB, BS, Brooklyn, NY
MANALAN, Allan S., MD, Indianapolis, IN
MANER, Thompson C., MD, Gainesville, FL
MARR, Kendall C., MD, Los Angeles, CA
MEHTA, Harshad R., MB, BS, Philadelphia, PA
MIKELL, Frank L., Jr., MD, Apple Valley, MN
MIKOLICH, J. Ronald, MD, Decatur, GA
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MOKOTOFF, David M., MD, Houston, TX
MORRIS, David L., MD, Salt Lake City, UT
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MURPHY, Judith H., MD, Pittsburgh, PA
NACCARELLI, Gerald V., MD, Hershey, PA
NASSER, Maher M., MB, BCh, New Haven, CT
NATTEL, Stanley, MD, Indianapolis, IN
NIJEM, Richard J., MD, Martinez, GA
NIKAM, Sriniuas G., MB, BS, Taylor, MI
NOLEWAJKA, Andre J., MD, Canada
O'CONNELL, John B., MD, North Riverside, IL
O'DONNELL, Jacqueline A., MD, Indianapolis, IN
OAKLEY, Robert F., MD, Galveston, TX
OREN, Micha, MD, Cambridge, MA
ORIEL, Robert J., MD, Allentown, PA
OSBAKKEN, Mary D., MD, PhD, Philadelphia, PA
OZNER, Michael D., MD, Mt. View, CA
PANETTA, Frank, MB, BS, Chicago, IL
PANG, Derek K. H., MD, Galveston, TX
PARIKH, Vrajmohan C., MB, BS, Detroit, MI
PASSALACQUA, Dominick J., MD, Brooklyn, NY
PATTERSON, William D., MD, PhD, Birmingham, AL
POTU, Ranganatha P., MB, BS, Brooklyn, NY
RAO, Adiraju V., MB, BS, Philadelphia, PA
RAVITSKY, Michael, DO, West Palm Beach, FL
REDER, Robert F., MD, New York, NY
REUBEN, Charles F., MD, Brookfield, WI
RICHARDSON, James A., MD, PhD, Irving, TX
ROBINSON, Anita E., MD, Somerville, MA
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ROLLER, Dean H., MD, Branford, CT
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ROTHKOPF, Michael, MD, Dallas, TX
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SAHOTA, Harvinder, MB, BS, Pasadena, CA
SAMANT, Anil R., MB, BS, Phoenix, AZ
SCHAEFFER, Jeffrey P., MD, Forest Hills, NY
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SOLBERG, Lloyd E., MD, PhD, Rochester, MN
SROUJIEH, Khaldoun S., MB, BCh, Richmond Heights, OH
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STARK, Robert M., MD, Bethesda, MD
STRASBERG, Boris, MD, Chicago, IL
SURDAKOWSKI, Francis P., MD, Brooklyn, NY
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TELLES, John G., MD, Rancho Palos Verdes, CA
THIRUVENGADAM, Arunachalam, MB, BS, San Francisco, CA
TICARIC, Stephen T., MD, Antioch, TN
TIWARI, Ratan L., MB, BS, Brooklyn, NY
TRUAX, James A., MD, Tampa, FL
VALDES, Mariano, MD, Spain
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VASUDEVA, Rekha, MB, BS, Pontiac, MI
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The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

NOVEMBER 1978 THROUGH FEBRUARY 1979

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

Nov. 2–4 — **New Techniques and Concepts in Cardiology. Coronary Artery Disease: Noninvasive Diagnosis, Cardiac Rehabilitation, Pharmacologic Treatment, Control of Risk Factors and Role of Surgery.** Stephen E. Epstein, FACC, director, Hyatt Regency Hotel, Washington, DC

NOV. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

DEC 2–4 — **Advances in Heart Disease 1979.** Dean T. Mason, FACC, director, Fairmont Hotel, San Francisco, CA

DEC. 3–6 — **Coronary, Hypertensive, Valvular and Myocardial Heart Diseases: The Multidisciplinary Approach.** William C. Roberts, FACC, director, The Williamsburg Conference Center, Williamsburg Lodge, Williamsburg, VA

DEC. 8–10 — **Eleventh Annual Cardiovascular Symposium: Patient Oriented Management of Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, NY

DEC. 11–14 — **Core Curriculum: Interpretation and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, directors. Philadelphia Marriott Motor Hotel, Philadelphia, PA

1979

JAN. 15–19 — **Tenth Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Robert F. Grover, FACC and Bruce C. Paton, FACC, co-directors. Snowmass Resort, Snowmass, CO

FEB. 2–4 — **New Concepts in Clinical Electrocardiography.** William J. Mandel, FACC, and H. J. C. Swan, FACC, directors. Beverly Hilton Hotel, Los Angeles, CA

FEB. 14–16 — **Cardiovascular Disease—1979: Advances in Diagnosis and Management.** Kirk L. Peterson, FACC, John Ross, Jr., FACC, Ralph Shabetai, FACC, Allen D. Johnson, FACC and Gabriel Gregoratos, FACC, directors. Sheraton Harbor Island Hotel, San Diego, CA

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning, Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

NOVEMBER 1978 THROUGH FEBRUARY 1979

Month/Dates	Course Director	Title of Program
1978		
November 6–9	Ralph Shabetai, MD, FACC	**Pericardial and Myocardial Diseases: Identification, Interaction, and Clinical Significance**
December 4–6	Borys Surawicz, MD, FACC	**Advanced Cardiac Electrophysiology and Electrocardiography**
December 11–13	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**
1979		
January 24–26	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**
January 29–31	William C. Roberts, MD, FACC	**Congenital Heart Disease: The Multi-disciplinary Approach**
February 7–9	Robert S. Eliot, MD, FACC	**Coronary Artery Disease: Angina and Myocardial Infarction**
February 15–17	J. Willis Hurst, MD, FACC	**Controversies in Coronary Disease**
February 19–21	Sylvan L. Weinberg, MD, FACC	**CCU Update for Nursing Supervisors**
February 26–March 1	R. Joe Noble, MD, FACC	**Update in Cardiology**

28th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Miami Beach, Florida **March 11–15, 1979**

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THE WHOLE PAPER

- Address manuscript to Managing Editor, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- Submit two copies of all elements of the article: text, references, legends, tables and figures.
- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
- Type all matter: (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on one side of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

THE TITLE PAGE

- Include first names, degrees and, where applicable, FACC for all authors.
- Provide a short running title of 3 to 6 words.
- Insert at bottom: name and address of institution from which work originated plus information about grants.
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- Limit words as follows: 100 to 250 words for major articles; 50 to 100 words for case reports.
- Add at end of abstract: list of 2 to 6 key words and subjects for indexing.

THE TEXT

- Type in duplicate; double-space.
- Do not use abbreviations such as SVC, WPW: write out superior vena cava, Wolff-Parkinson-White.
- Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.
- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
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- Provide concluding page numbers for all journal references and specific page numbers for all book references. Indicate all abstracts by the abbreviation (abstr).
- Follow the general arrangement, abbreviations and punctuation styles shown below.

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- Identify at the end of each legend and in alphabetical order all abbreviations in the figure described.

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31. Vismara LA, Vera Z, Miller RR, Mason DT: Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 39:1027–1034, 1977

(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

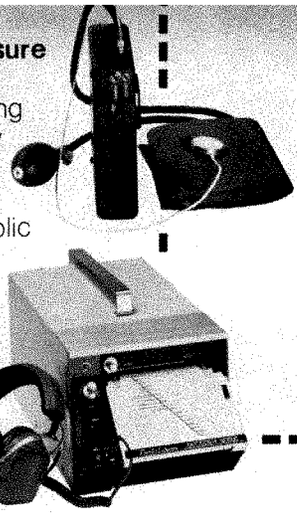
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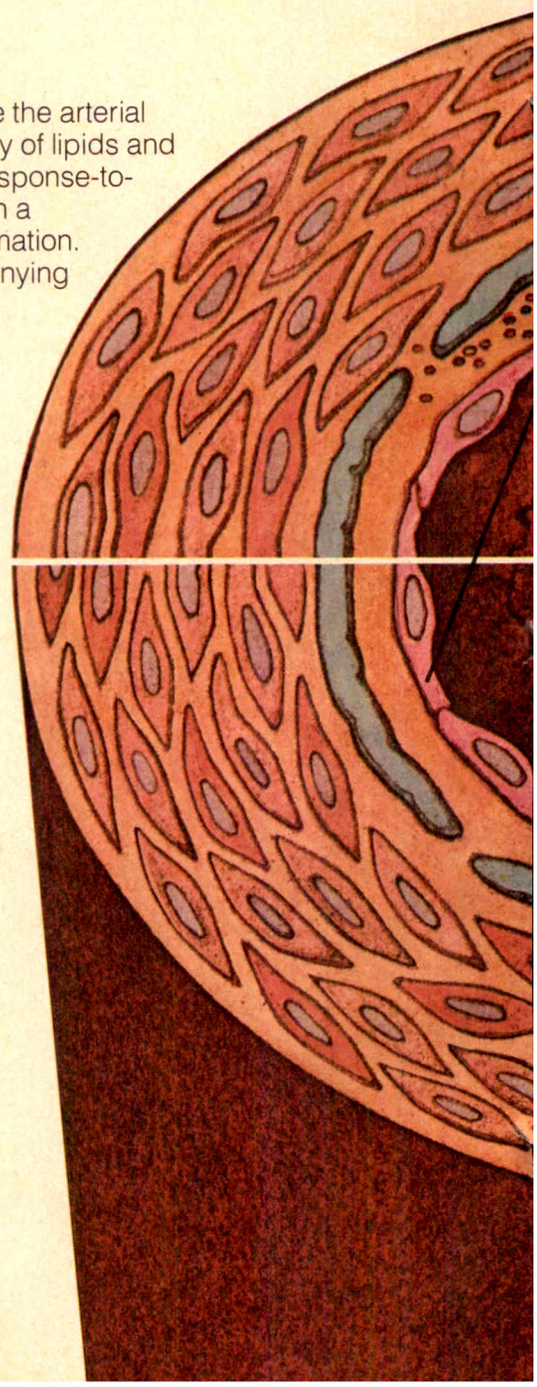
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New Horizons in Hyperlipidemia

HIGH BLOOD PRESSURE & ELEVATED LIPIDS: PARTNERS IN PATHOLOGY

Hypertension and hyperlipidemia working in tandem can damage the arterial endothelium—the thin barrier that selectively prevents undue entry of lipids and other blood constituents into the arterial wall. According to the "response-to-injury" hypothesis,[1-3] a break in the endothelium is the first event in a pathologic sequence that can ultimately lead to arterial lesion formation. (See more detailed explanation of this hypothesis in the accompanying schematic illustration at right.)



Endothelial injury: a component of arterial response to hypertension

Animal and human studies[3,4] demonstrate that hypertension can injure the arterial endothelium. The damage seems to be related as much to local hemodynamic stresses at sites of vessel bending or branching[4,5] as to the height of the pressure. It has also been shown that the arterial intima is more permeable to plasma lipoproteins in hypertensive individuals than in normotensives.[6]

Chronic hyperlipidemia: a factor in initiating and maintaining lesions

In addition to causing lipid deposition in arterial plaques,[5] hyperlipidemia may be an initiating factor in lesion formation.[1] There is also evidence (from primate studies) that elevated serum lipid levels may inhibit the "normal" regression of arterial lesions following a single injury to the endothelium.[1]

1. Ross, R., and Harker, L.: Science *193*:1094 (Sept.) 1976.
2. Ross, R., and Glomset, J. A.: N. Engl. J. Med. *295*:420 (Aug. 19) 1976.
3. Schwartz, S. M.: Cardiovasc. Med. *2*:991 (Oct.) 1977.
4. Glagov, S.: Med. Clin. North Am. *57*:63 (Jan.) 1973.
5. DiGirolamo, M., and Schlant, R. C., in Hurst, J. W., *et al.* (eds.): The Heart, 4th ed., New York, McGraw-Hill, 1978, pp. 1114, 1116.
6. Smith, E. B., and Slater, R. S., in Atherogenesis: Initiating Factors, CIBA Foundation Symposium *12*:39, 1973.

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1

In the normal arterial vessel, the endothelial layer is intact, able to perform its function as partial barrier to the entry of excessive amounts of lipids and other serum constituents into the arterial wall.

2

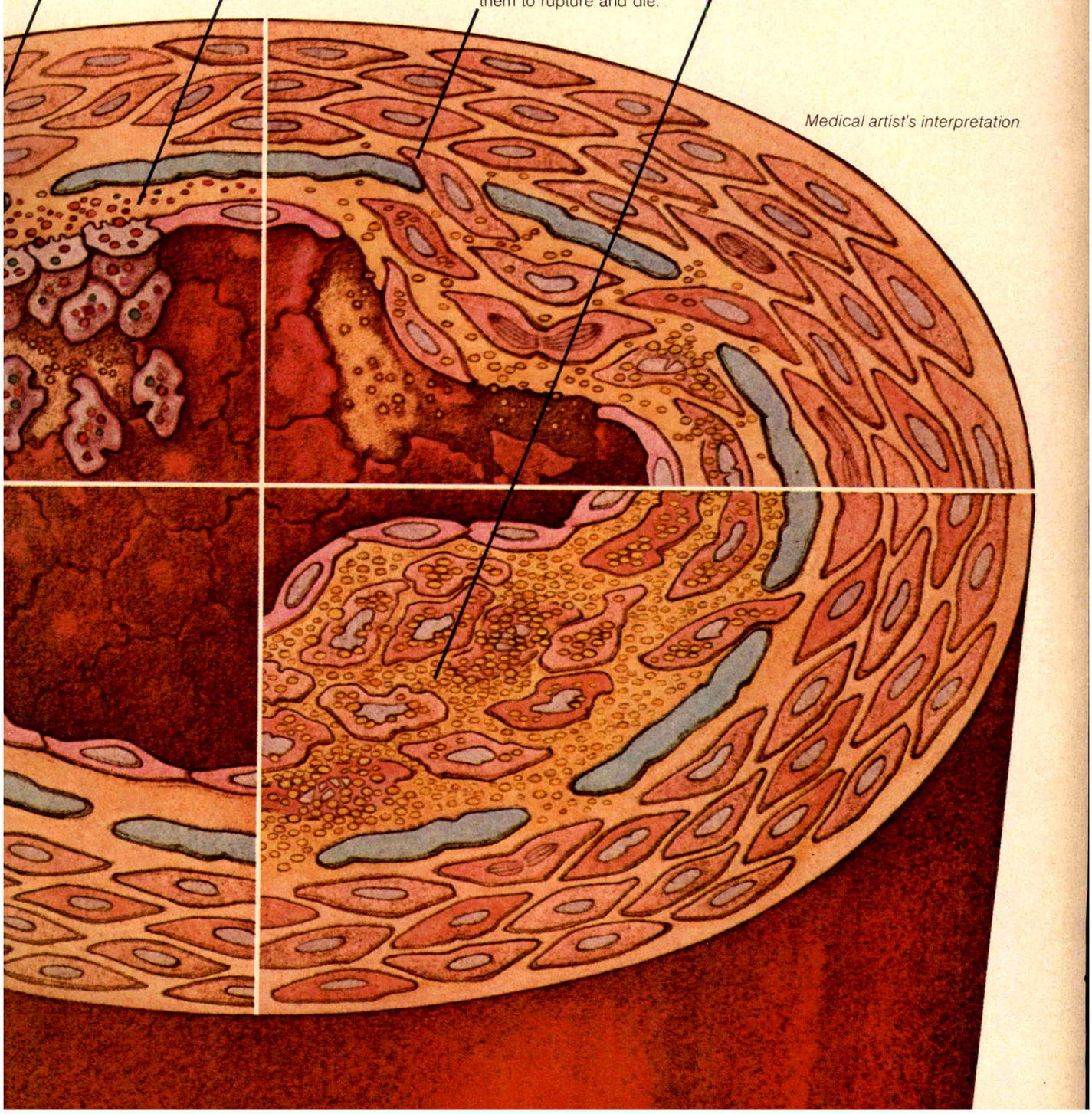
Endothelial injury, resulting from elevated blood pressure and/or high serum lipid concentrations, reduces the effectiveness of this barrier. Serum lipids can then more easily infiltrate subendothelial connective tissue as can factors released from platelet granules after the platelets have adhered to the subendothelial collagen.

3

Smooth muscle cell proliferation is stimulated by platelet mitogenic factors, plasma lipoproteins and other plasma constituents. The cells migrate from the media of the vessel into the intima, where they continue to multiply. Endothelial cells regenerate to cover the exposed intima. Concurrently, in hyperlipidemic individuals, arterial smooth muscle cells are exposed to, and may internalize, large amounts of lipid substances which eventually can cause them to rupture and die.

4

The characteristic arterial lesion shown here is the product of smooth muscle cell proliferation, accumulation of intracellular and extracellular lipids, and debris from muscle cell necrosis. This is the end result of *chronic* or *repeated* endothelial injury. In contrast, the single or widely separated instances of endothelial damage that occur in all persons at varying times usually allow for lesion regression and repair.



Medical artist's interpretation

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1. Title of publication: THE AMERICAN JOURNAL OF CARDIOLOGY.

1A. Publication No. 544400.

2. Date of filing: October 1, 1978.

3. Frequency of issue: Monthly—except May—semi-monthly.

3A. No. of issues published annually: 13.

3B. Annual subscription price: $28.00 U.S.; $32.00 Canada; $40.00 Foreign.

4. Location of known office of publication: 666 Fifth Avenue, New York, N.Y. 10019.

5. Location of the headquarters or general business offices of the publishers: 666 Fifth nue, New York, N.Y. 10019.

6. Names and complete addresses of publisher, editor, and managing editor: Publisher: is F. LeJacq, 666 Fifth Avenue, New York, N.Y. 10019; Editor: Simon Dack, MD, 1111 Park nue, New York, N.Y. 10029; Managing Editor: Ruth R. Ohman, 666 Fifth Avenue, New k, N.Y. 10019.

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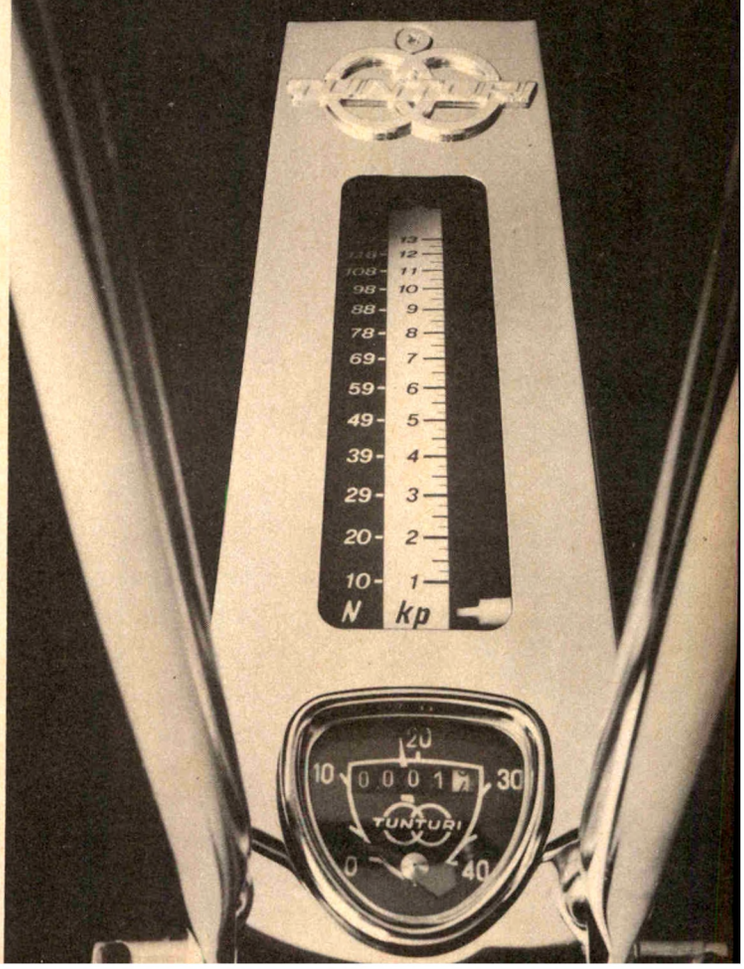
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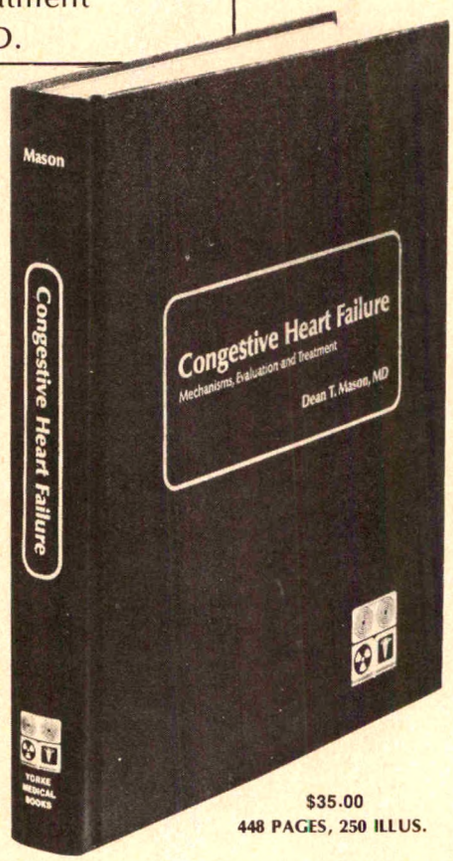


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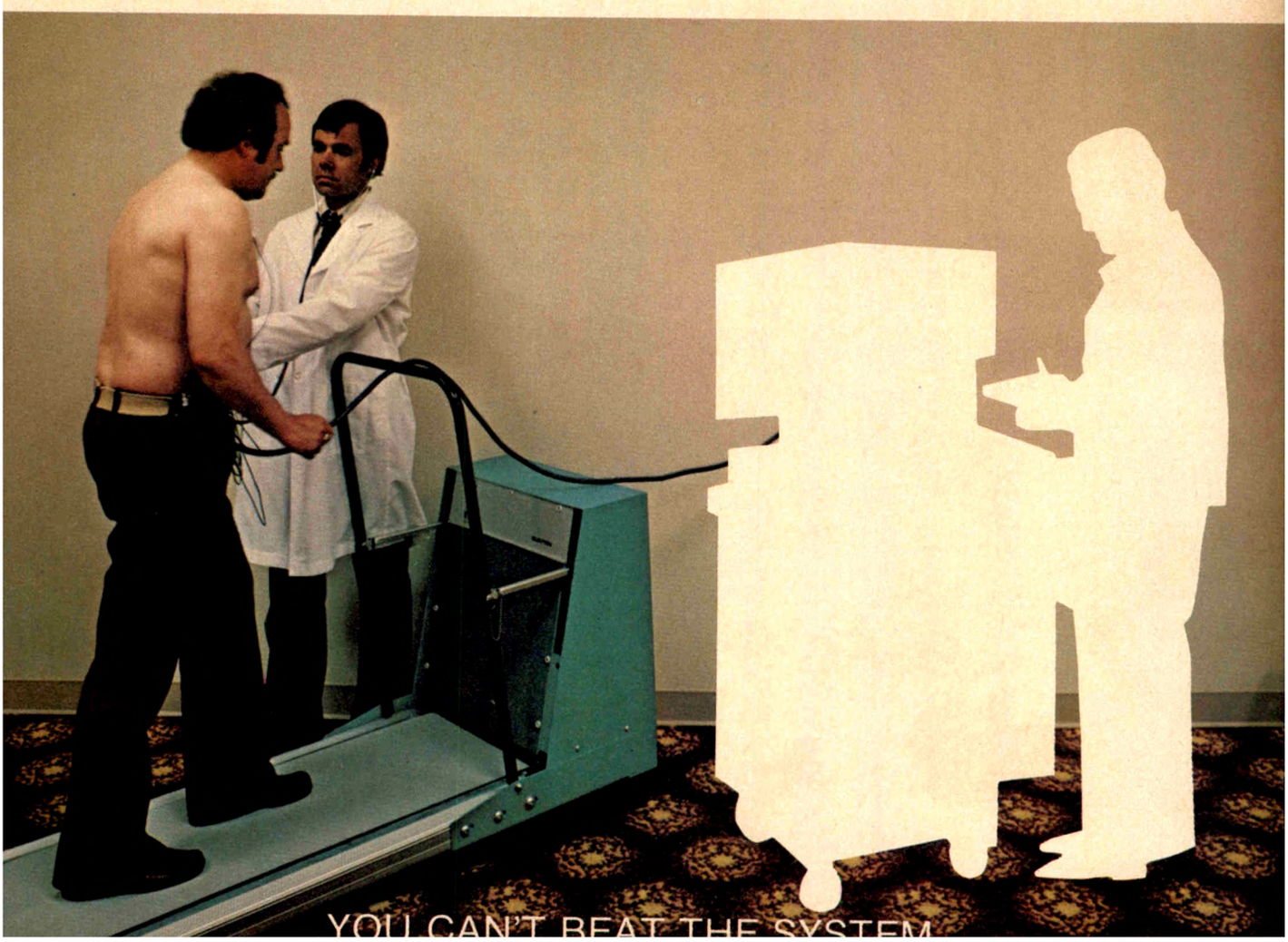
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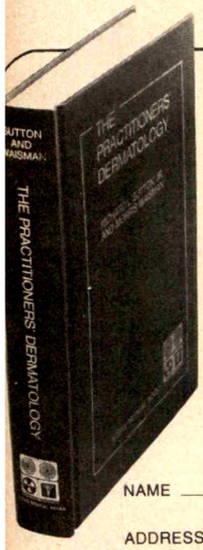
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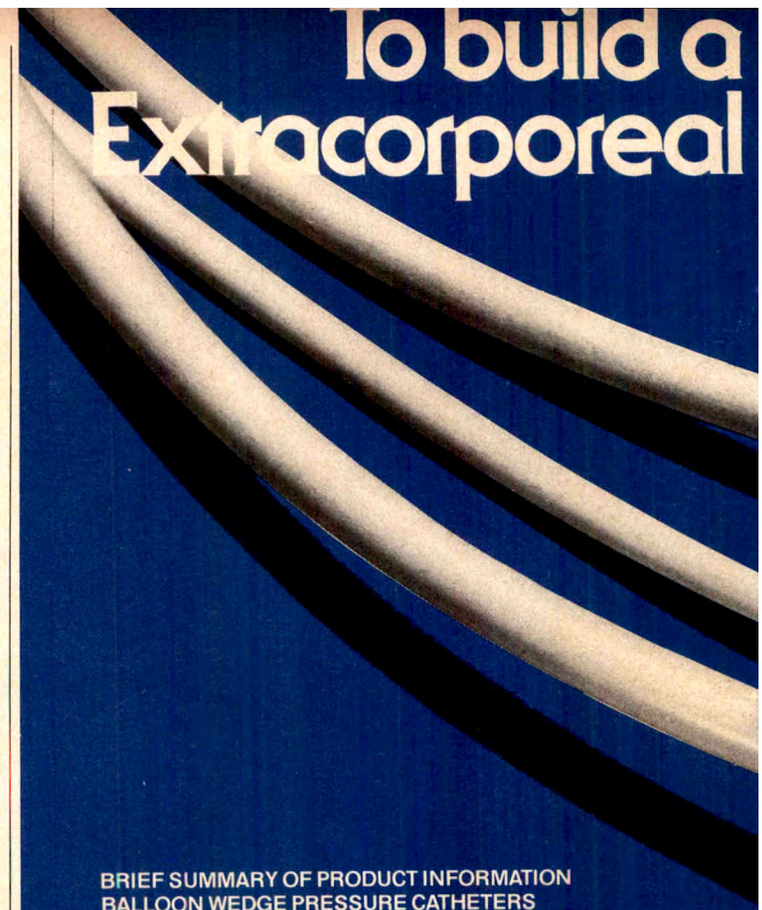
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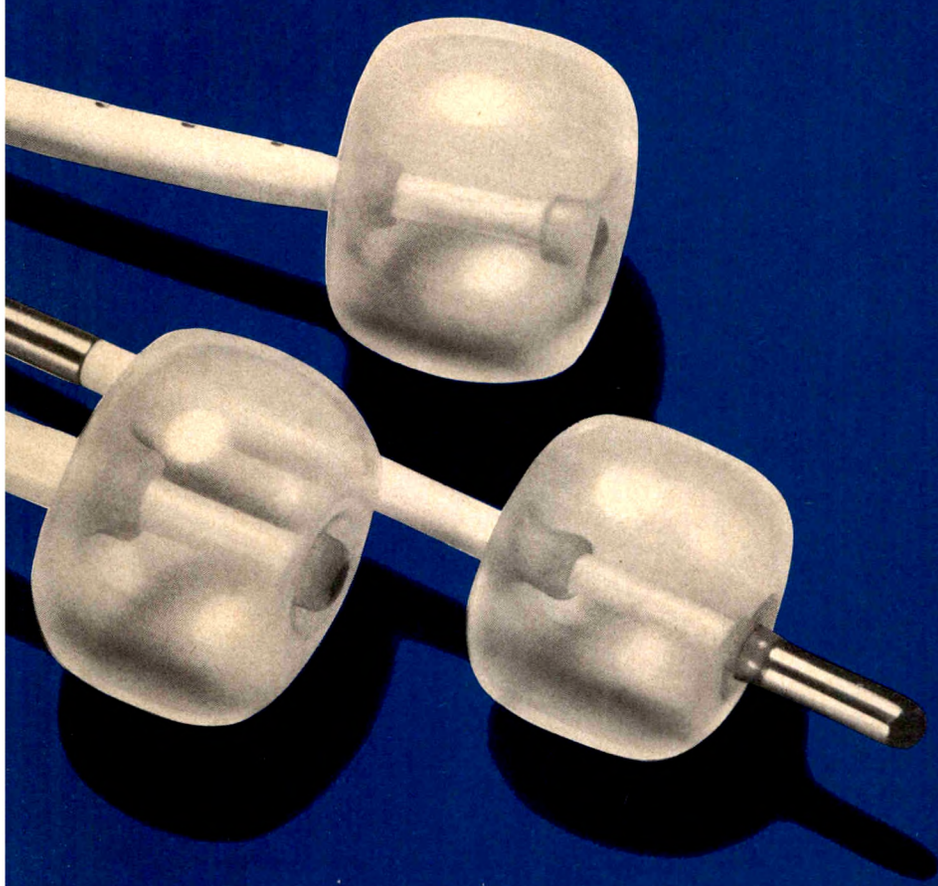
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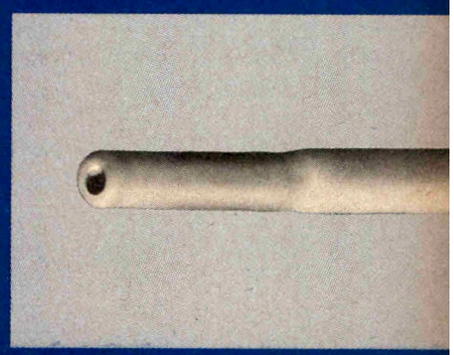
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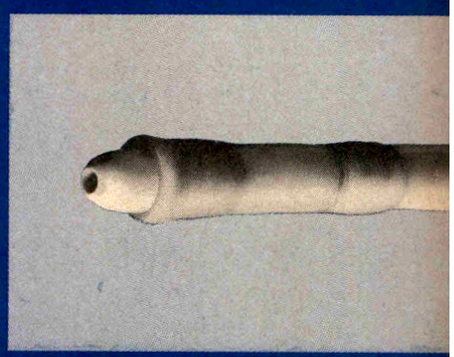
General Warnings: Carbon dioxide must be used to inflate balloon if there is a possibility that balloon rupture would result in air embolism in the left heart or systemic circulation. Do not inflate balloon beyond stated maximum inflation capacity. Exercise care when passing catheters in patients with left bundle-branch block because right bundle-branch block induced by traumatic catheter passage could result in complete heart block and asystole. **General Precautions:** Do not use liquids as balloon-inflation media. Pass catheter with continuous cardiographic monitoring and fluoroscopic guidance, and confirm final tip position by X-ray. Deflate balloon prior to withdrawing catheter to avoid possible valve damage. Use aseptic technique throughout procedure. All catheters are for single use only. Do not resterilize or reuse. Federal law (U.S.A.) restricts these devices to sale by or on the

better cardiac catheter, starts with a built-in tip.





The Extracorporeal built-in tip, balloon deflated.



Other manufacturer's built-on tip, balloon deflated.

As you can see, the Extracorporeal tip is smooth, tapered, unruffled, suture free, no wider than the catheter itself. The benefits are built-in:

- **The introducer is the same size as the catheter.*** Not larger. This means a smaller insertion hole and less likelihood of trauma and intimal damage. And it simplifies introducer selection.
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- **A smaller diameter catheter may be used,** because a larger lumen be matched only by a larger-diameter competitive catheter.
- **The tip is suture-free,** eliminating clotting caused by the sutures' irregular surface.

Beyond the tip, a host of other benefits.

- **Inflation is more convenient** because every Extracorporeal balloon catheter is packaged with an appropriately sized syringe.
- **Pure platinum electrodes for better electrical characteristics.** Blood may alter the conductivity properties of stainless steel and cause inferior readings. That's why our balloon pacing catheters employ only inert platinum for electrodes.
- **High pressure tubing** used in our Berman angiographic catheters when drugs or dye must be injecte
- **More sizes available.** Especially in Berman angiographic and wedge pressure models. And we can supply custom catheters, too.
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- **Our new brochure has all the facts.** Just let us know where you are and we'll send you one. Call your Extracorporeal representative, or write or call us toll free: 800-523-1740.

*With one small exception—the Extracorporeal 4F size uses a 4-1/2 size introducer.

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For nine and a half years Quinaglute® (quinidine gluconate) has kept the pace for Mary L.*

*Based on actual case history (photos posed by professional model).

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Time-proven for safety
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Time-proven for patient compliance
- convenient dosage schedule that's easy to remember: 1 to 2 Dura-Tabs® every 8 or 12 hours
- h.s. dose helps avoid early morning reversion

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.

Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances. 101-71

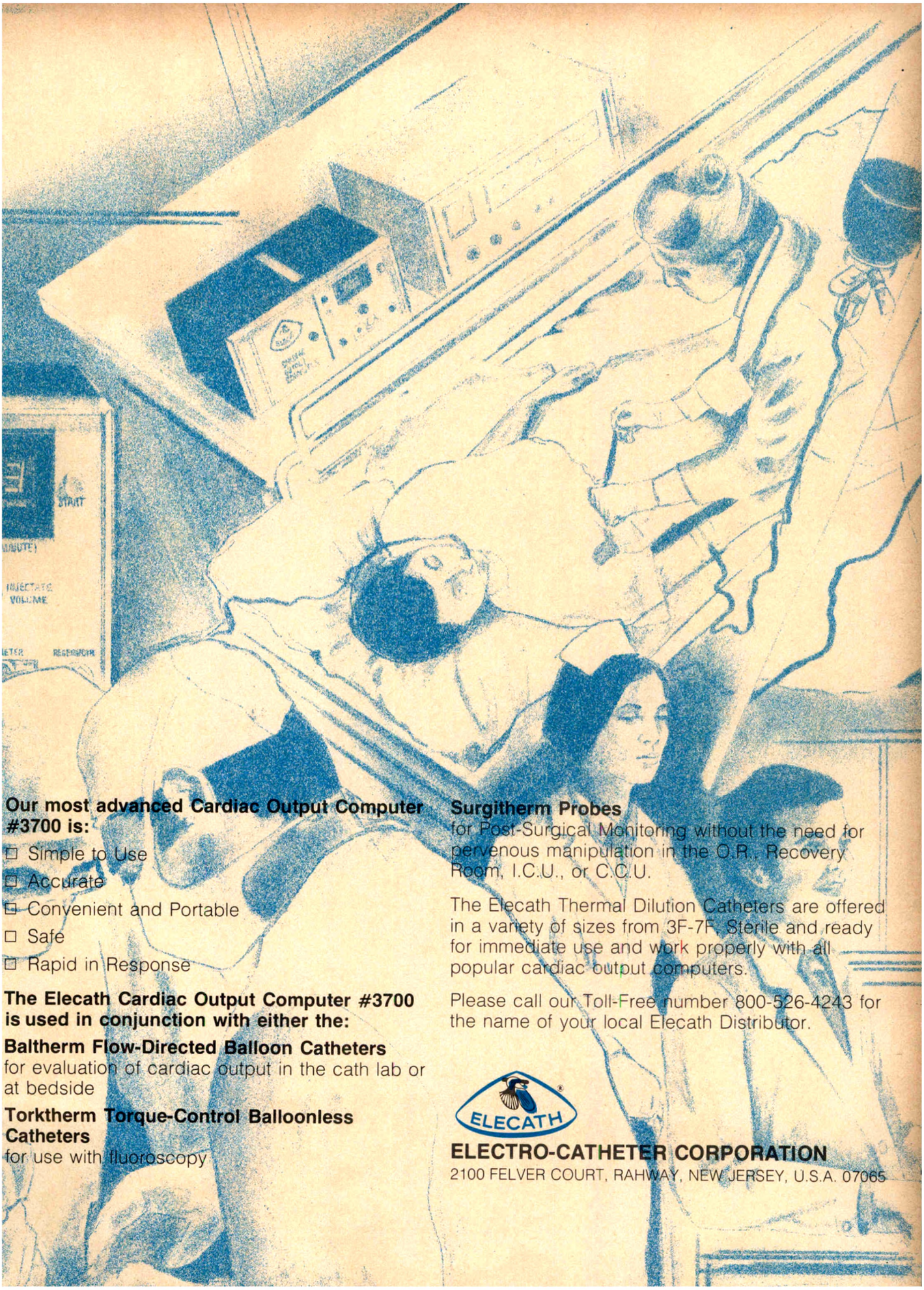
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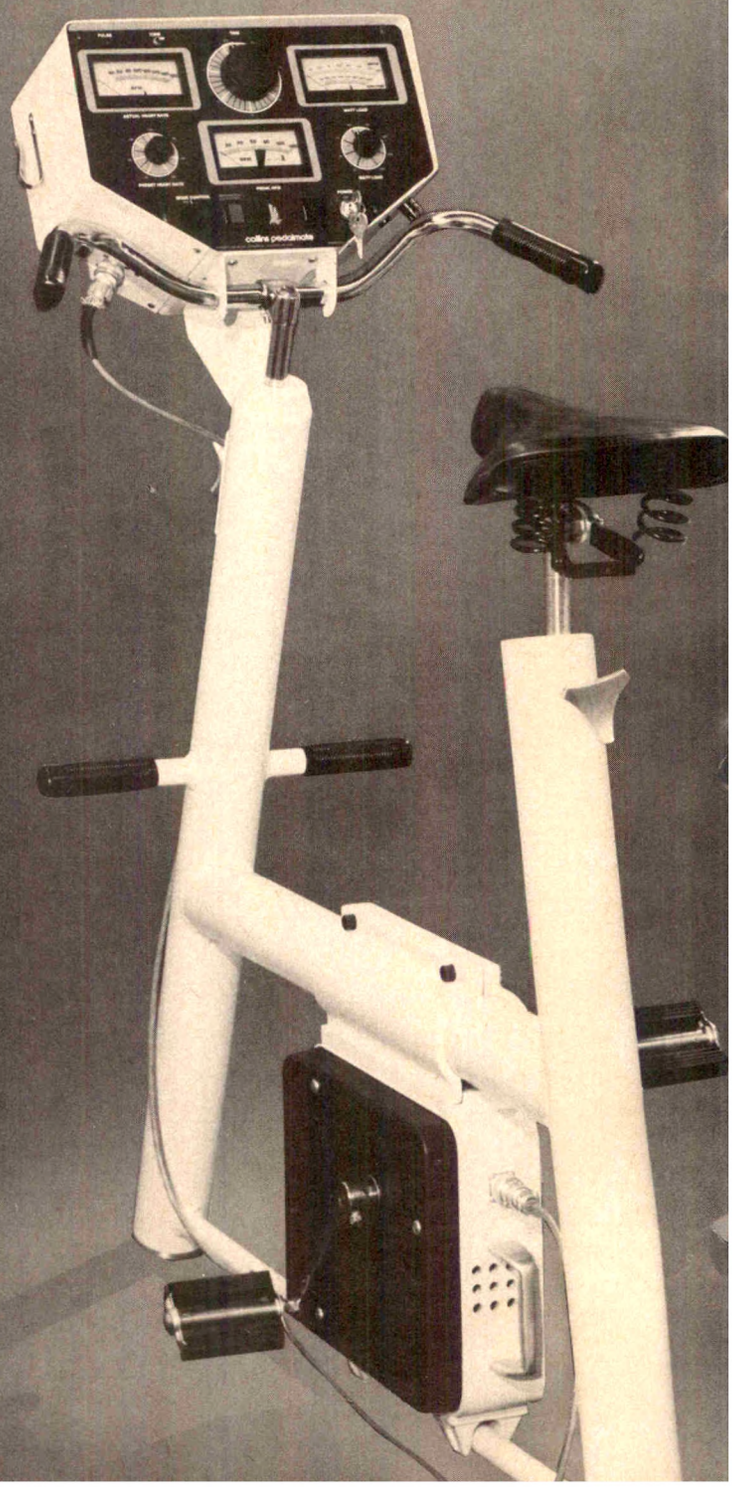
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The Pedalmate is an ergometer which offers two modes of operation. In the 'Heart Rate Control Mode,' the work load is automatically varied by means of a feedback control signal which is proportional to the difference between the subject's actual heart rate and a preset, selectable heart rate. The subject's actual heart rate is detected by a blood pressure wave transducer which attaches comfortably to the earlobe. The fine adjustment in work load makes it possible to exercise the subject at a preset heart rate level for a preselected time.

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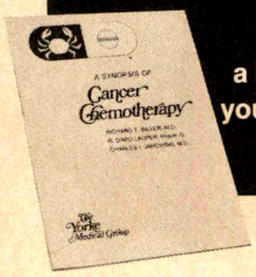
SPECIFICATIONS

Heart Rate Control Accuracy:	±5 BPM
Heart Rate Accuracy:	±2% of reading
Watt Load Accuracy:	±5% of reading
Pedal Rate Accuracy:	±2% of reading (0-120 rpm)
Heart Rate Range:	40 to 180 BPM
Watt Load Range:	25 to 200 watts (150 to 1200 KPM/min.)
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- Antibiotics
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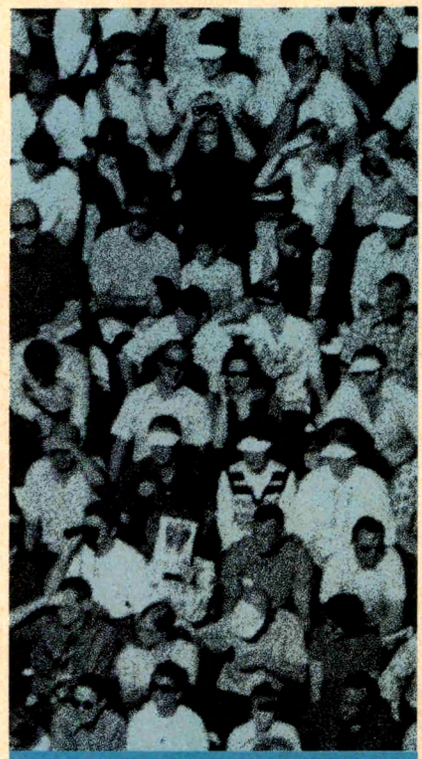
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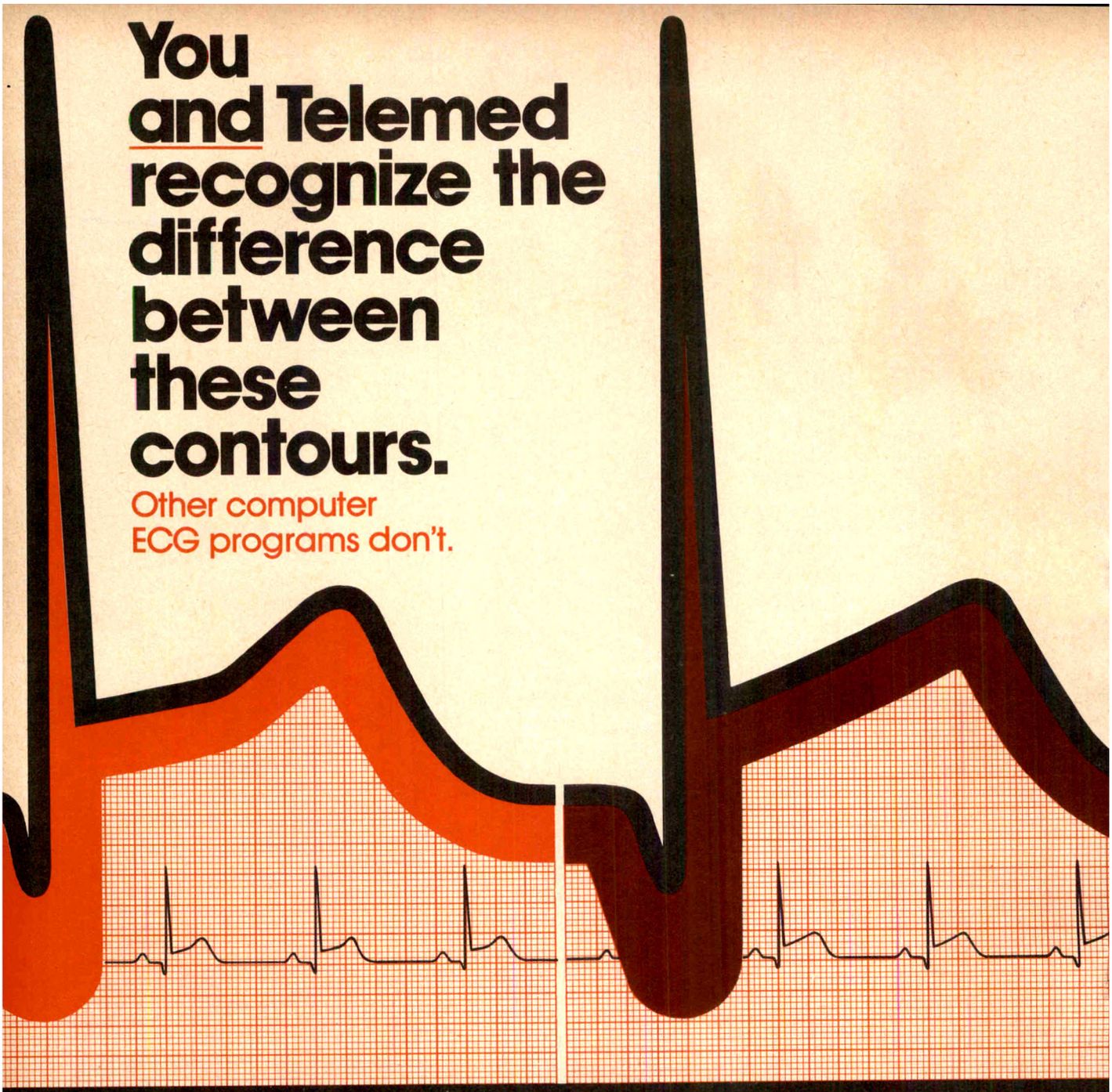
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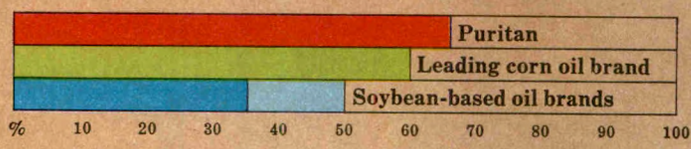
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A practical adjunct in serum cholesterol control

Puritan is the first major cooking oil made principally from highly polyunsaturated sunflower oil. The sunflower oil gives Puritan an edge in polyunsaturate levels over leading corn and soybean-based oils.

*** A comparison of polyunsaturate levels of major brands**



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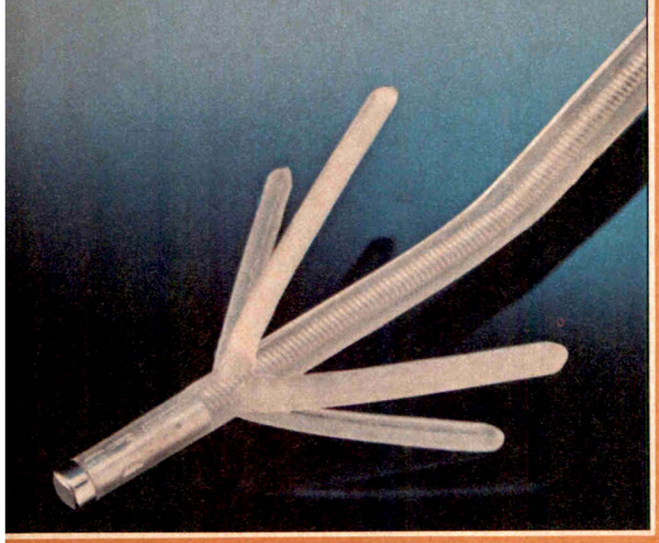


The nutrition department of a major university has published the results of a study[1] that evaluated a dietary serum-cholesterol-reducing program which included Puritan Oil. The study was conducted in a family situation—entire families used Puritan as part of a total serum-cholesterol-reducing diet. The data showed significant decreases in serum cholesterol levels among all participating groups. These lowered levels were reached within 10 days, and were maintained throughout the diet modification period.

Reference: 1. Witchi, J.C. et al., *J. Am. Dietetic Assoc. 72:* 384, 1978.

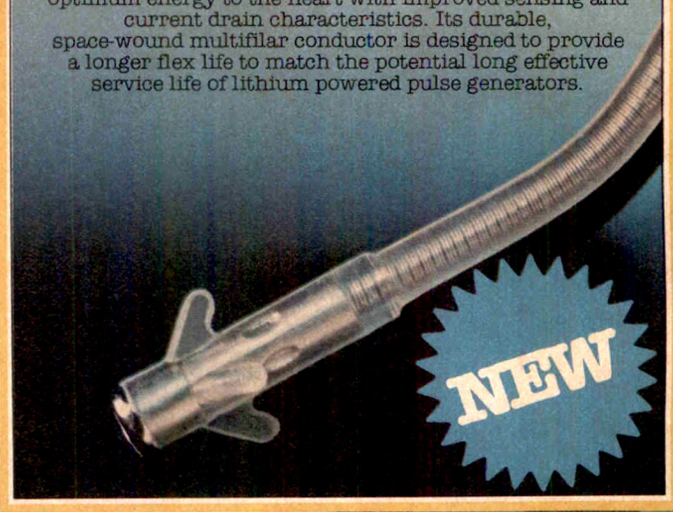
An Endocardial Tined Ventricular Lead.

The Medtronic ® 6950 and 6951 unipolar and bipolar tined leads feature four integral silicone rubber tines that protrude from the lead body just proximal to the tip electrode. These tines were designed to provide better acute lead stability and reduce chronic lead dislodgement by latching onto the papillary musculature or the trabeculae of the right ventricle. The large surface area provided by the tines should also enhance the stability afforded by fibrosis.



A Small, Durable Endocardial Tined Lead.

The newest members of the Tenax ™ family of self-anchoring leads – the 6961 and 6962 unipolar and bipolar leads – feature shorter, smaller tines and small tip diameter (8 French; approximately 10 French with tines folded) enabling the physician to use the more common cephalic approach. Though small, the soft, pliable tines are still long enough to become securely anchored in one or more of the interstitial spaces formed by the trabeculae of the right ventricular chamber. The lead's ring-tipped electrode provides optimum energy to the heart with improved sensing and current drain characteristics. Its durable, space-wound multifilar conductor is designed to provide a longer flex life to match the potential long effective service life of lithium powered pulse generators.



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Tenacious, positive-anchoring lead tips.
Tips designed to minimize dislodgement problems
associated with standard endocardial pacing leads.
Tips that stay where you put them.

EDTRONIC IMPLANTABLE PACING LEADS

tended Use

dtronic implantable pacing leads are designed to be used with Medtronic pulse nerators as part of a cardiac pacing system (see product labeling for specific directions garding applications).

ntraindications

docardial pacing leads are contraindicated in the presence of tricuspid valvular disease.

Myocardial leads are contraindicated for a patient whose myocardium is thin-walled, suffused with fat, or infarcted in the area of electrode placement.

Myocardial leads may be contraindicated in the older high risk patients with a low tolerance to general anesthesia.

Atrial J-leads are contraindicated in the absence of a right atrial appendage.

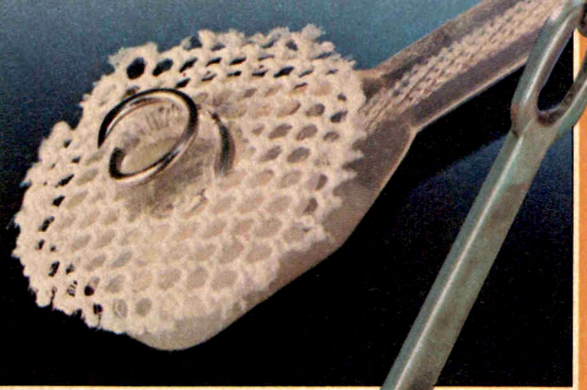
Warnings

An implanted lead constitutes a direct, low resistance current path to the myocardium.

C 78-AD-0012

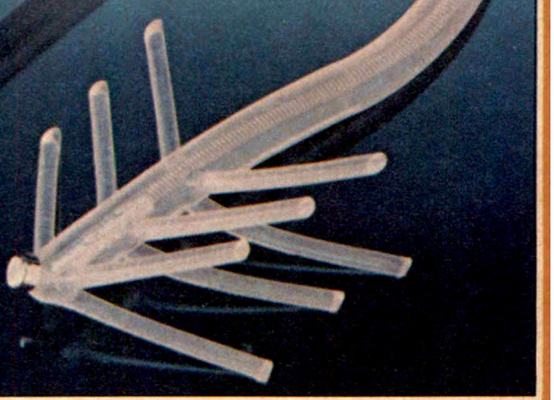
A Unique Sutureless Myocardial Lead.

Our Model 6917 sutureless lead is the largest selling pacing lead worldwide. Its unique screw-in electrode, introduced in 1973, eliminates the necessity of making a stab wound and suturing to the myocardium. The electrode tip is secured by simply rotating it into the myocardium. The 6917A has been successfully installed on either the right or left ventricle using a variety of surgical approaches such as limited thoracotomy, subxiphoid, transxiphoid, and transmediastinal, in some cases using only local anesthesia.



A Tined Endocardial Atrial J-Shaped Lead.

The Medtronic 6991 unipolar and 6990 bipolar leads are molded into a J configuration to facilitate placement and lodging into the right atrial appendage. During insertion, the J tip is straightened by means of lead stylets. The distal end of the J contains a series of nine silicone rubber tines; the electrode tip is canted inward so the force exerted by the tines will enable the electrode to contact the endocardial surface of the atrium. After the lead tip has been advanced into the desired position, the stylets are partially withdrawn to allow the lead to assume its natural J shape. The tines are fixed into the atrial appendage by becoming anchored in one or more of the interstitial spaces formed by trabeculae.



For further information on the Medtronic Tenax™ lead family, contact your Medtronic, Inc. representative or write for a complete technical brochure.

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uring the connection and testing procedures, only battery-powered pulse generators
hould be used with the lead system to protect against ventricular fibrillation induced by
ternating current leakage. Extreme caution must be taken to properly ground all
ne-powered equipment used in the vicinity of the patient.

recautions

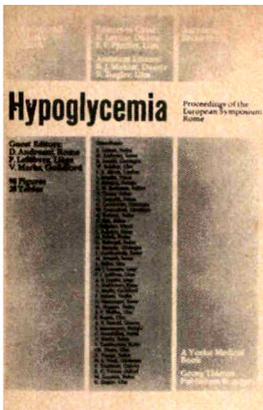
he pacing system may cease to function due to lead-related problems such as
splacement, fracture, fibrotic tissue formation and elevated thresholds.

Side Effects

Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis, embolism.

How Supplied

Medtronic permanent implantable leads are supplied sterilized and individually wrapped. Medtronic pacing leads are designed to be used with Medtronic pulse generators.



One of the Most Frequently Overdiagnosed Diseases!

■ *Here at last is an objective study of essential reactive hypoglycemia . . . definition, recognition, pathology, etiology, and treatment.*

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P. Lefèbvre, MD, Dept. of Medicine, University of Liège
V. Marks, DM, Prof., Dept. of Biochemistry, Univ. of Surrey

This European (Rome) Symposium was the first free interchange of ideas among scientists in the various medical disciplines—physiology, internal medicine, endocrinology, clinical biochemistry, etc.—necessary to the understanding, diagnosis and treatment of hypoglycemia. The concentration was on the various aspects of insulin-producing tumors and the vexed question of essential reactive hypoglycemia. Special attention was given to the widespread misinterpretation of laboratory data relating to the prolonged oral glucose test which has resulted in the erroneous belief that "millions suffer from hypoglycemia."

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hydrochlorothiazide 25 mg.)

WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

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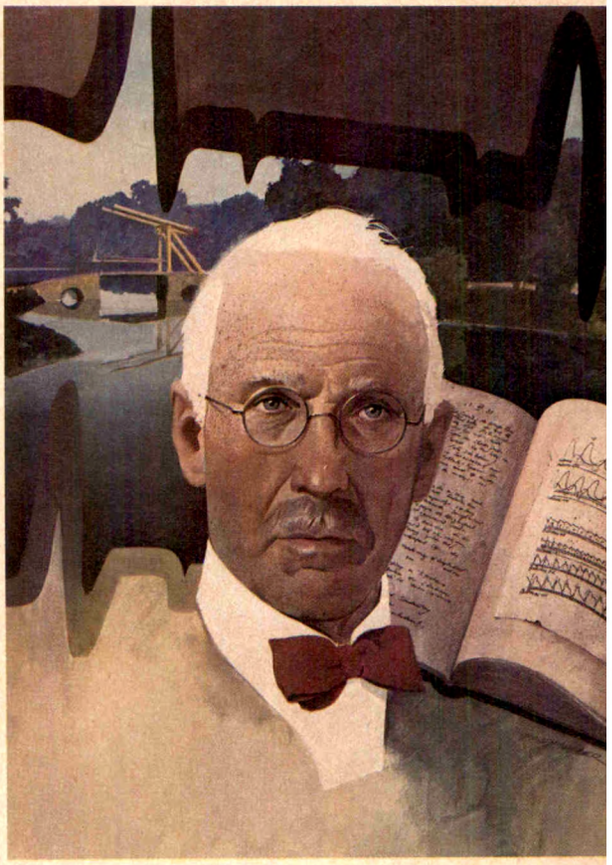
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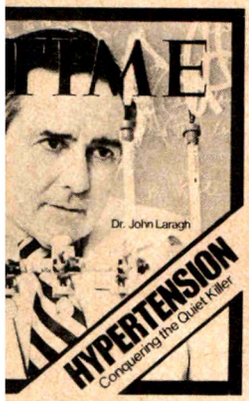
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classic treatise for understanding, diagnosis, treatment

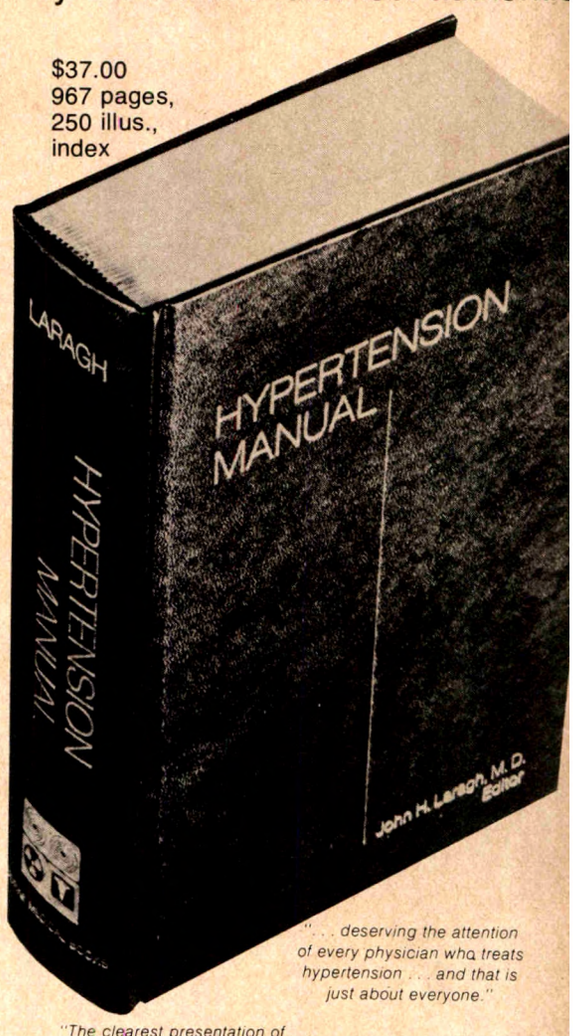


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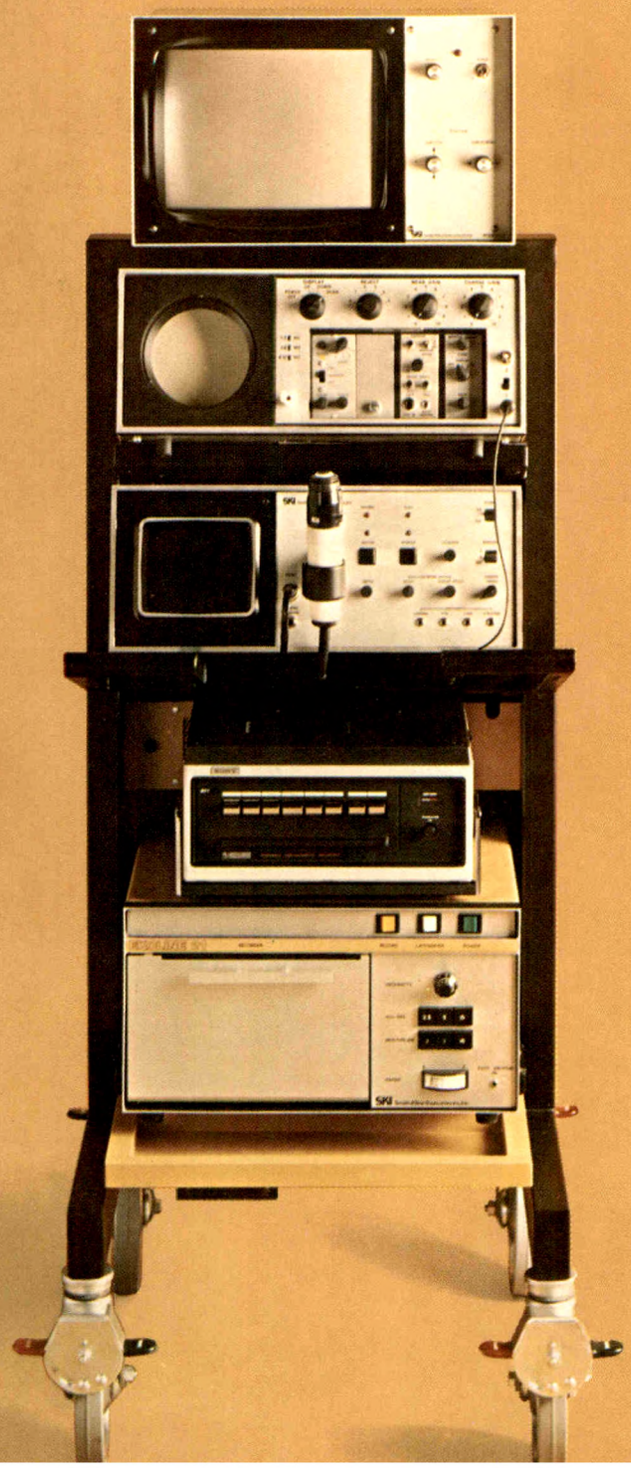
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- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion— only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

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DECEMBER 1978

The American Journal of CARDIOLOGY®



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Right Ventricular Infarction

The Pericardium

Variant Angina

Volume Index

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logical therapy for the vast
who need more or other



Logical therapy because essential hypertension is usually characterized by elevated peripheral resistance with normal cardiac output. ALDOMET lowers blood pressure apparently by lowering peripheral resistance—while cardiac output is usually maintained.

Appropriate for all degrees of hypertension when drug therapy is required

Highly effective in mild, moderate, or severe hypertension, ALDOMET (Methyldopa, MSD) is useful when there has been an inadequate response to initial thiazide therapy, or as initial therapy when thiazides are deemed inappropriate or contraindicated (for example, when hypersensitivity to sulfonamide-derived drugs exists).

Appropriate for many hypertensive patients requiring special consideration

- hypertensive patients with renal impairment—ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. (Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.)
- hypertensive children requiring drug therapy (See pediatric dosage recommendations in the addendum on the last page of this advertisement.)

Not contraindicated in the following coexisting conditions in which some other antihypertensives are contraindicated

- congestive heart failure (Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses methyldopa should be discontinued.)
- coronary artery disease (Aggravation of angina pectoris may occur with ALDOMET.)
- mitral valvular rheumatic heart disease
- bronchial asthma
- allergic rhinitis during the pollen season
- greater than first-degree heart block
- active peptic ulcer
- ulcerative colitis

majority of hypertensives
therapy than a thiazide...



Therapeutic limitations

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, please see the brief summary of prescribing information.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

Logical therapy for the vast majority of hypertensives who need more or other therapy than a thiazide

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

J8AM17(709)

addendum

MSD
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DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- if effective control of blood pressure cannot be maintained on 2.0 g methyldopa daily and a thiazide is not already part of the regimen, a thiazide should be added
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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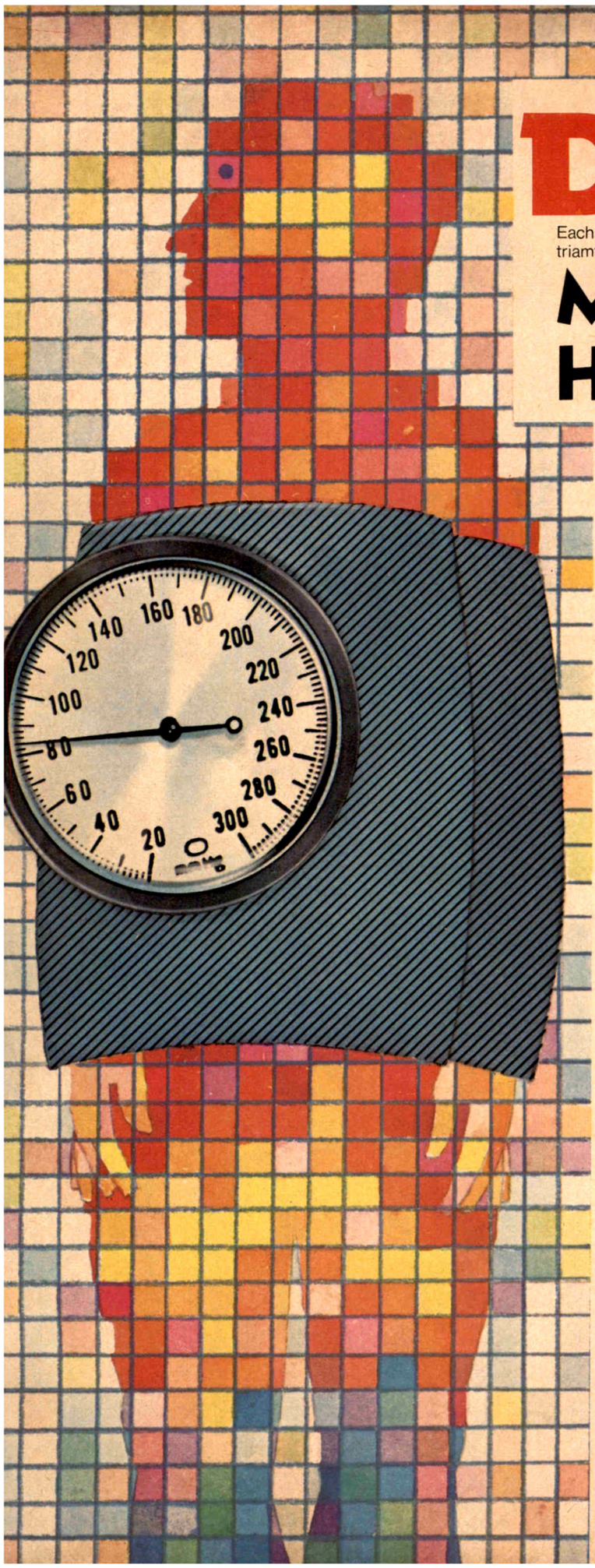
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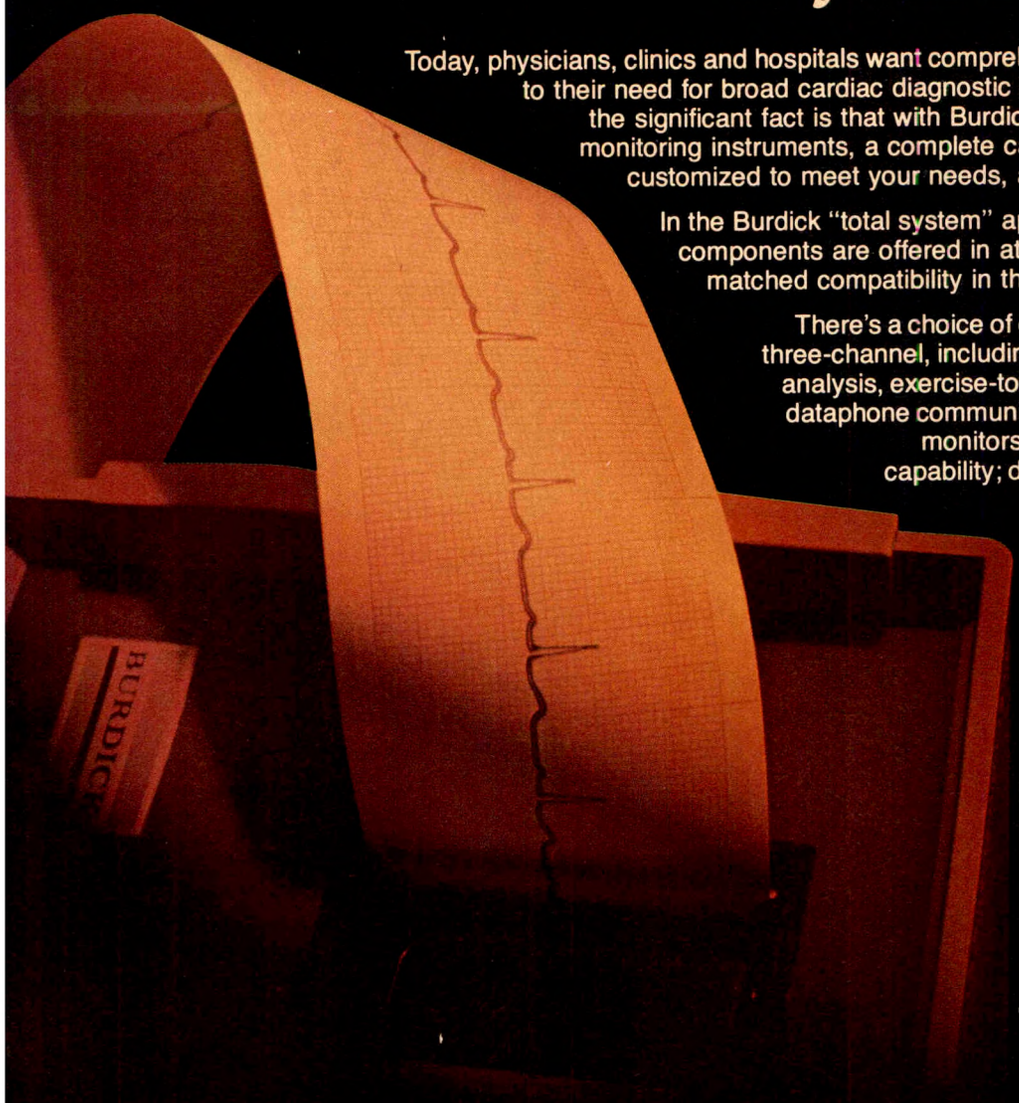
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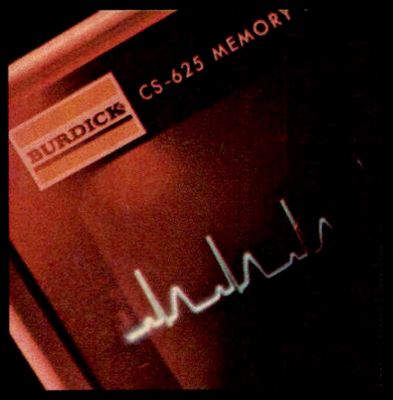
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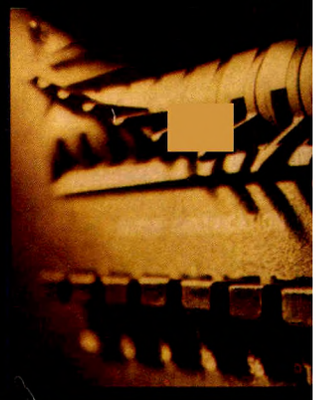
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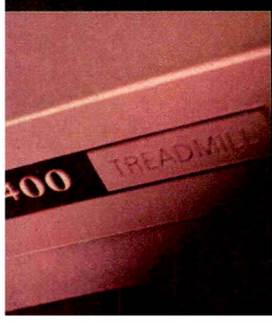
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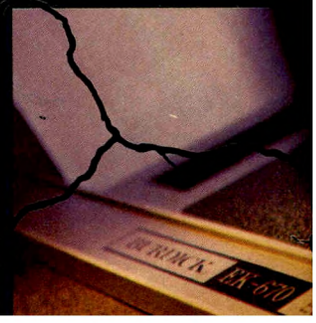




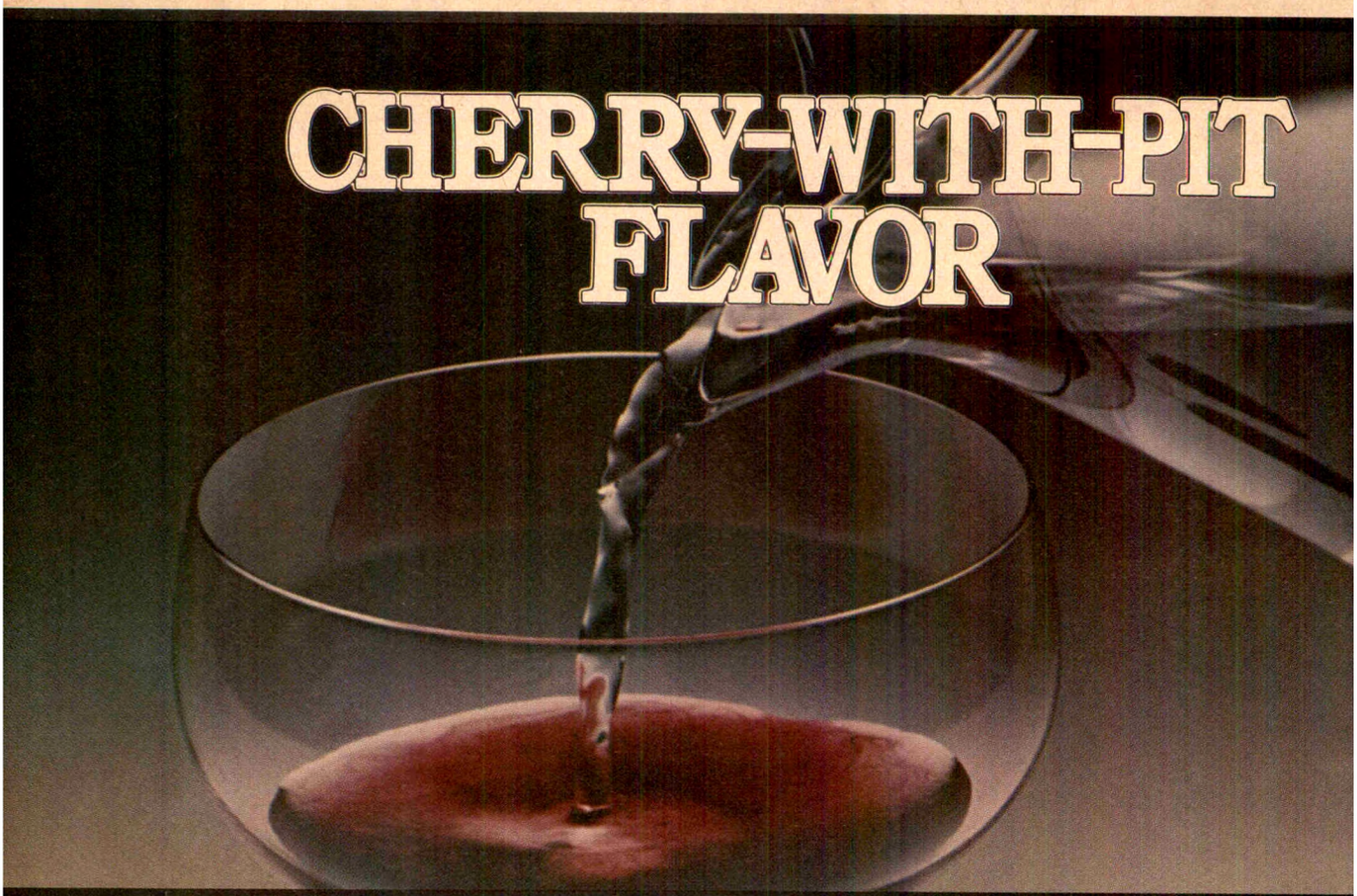








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Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

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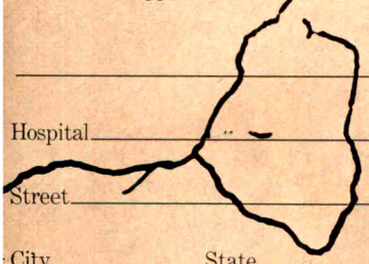
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CLINICAL STUDIES

885 **Right Ventricular Infarction Complicating Left Ventricular Infarction Secondary to Coronary Heart Disease. Frequency, Location, Associated Findings and Significance From Analysis of 236 Necropsy Patients With Acute or Healed Myocardial Infarction**

JEFFREY M. ISNER and WILLIAM C. ROBERTS

Postmortem data in a series of 236 patients with transmural myocardial infarction showed that right ventricular infarction had an incidence rate of 14 percent and occurred exclusively as a complication of posterior left ventricular infarction with transmural infarction of the posterior septum. Nearly 25 percent of the patients with posterior wall infarction of the left ventricle had associated infarction of the right ventricle, generally in its posterior free wall. Clinical evidence of posterior left ventricular infarction and right ventricular dilatation should alert one to the presence of right ventricular infarction. The hemodynamic profile considered characteristic of right ventricular infarction is less diagnostically sensitive than thought, and right ventricular infarction may occur in the presence of normal or near normal intracardiac pressures.

895 **Correlation Between Myocardial Structure and Diastolic Properties of the Heart in Chronic Aortic Valve Disease: Effects of Corrective Surgery**

FRANZ SCHWARZ, WILLEM FLAMENG, JUTTA SCHAPER and FRITZ HEHRLEIN

This study of left ventricular end-diastolic properties before and 6 months after aortic valve replacement with a Björk-Shiley prosthesis revealed reduction and normalization of both elastic stiffness of the left ventricle and mean left atrial pressure in most patients after surgery. Close correlations were obtained between myocardial cell diameter and end-diastolic pressure, end-diastolic wall thickness and stiffness constant and between mean left atrial pressure and elastic stiffness. There was no significant correlation of these variables with percent fibrosis. These results suggest that myocardial cell diameter rather than myocardial fibrosis is a major determinant of end-diastolic properties of the left ventricle in chronic aortic valve disease. Aortic valve replacement with a Björk-Shiley prosthesis, which produces less outflow tract obstruction than the Starr-Edwards prosthesis, normalized diastolic cardiac function and revealed a great adaptive power of the hypertrophied myocardium.

904 **Localization of Pericardial Effusion With Wide Angle Phased Array Echocardiography**

RANDOLPH P. MARTIN, HARRY RAKOWSKI, JAMES FRENCH and RICHARD L. POPP

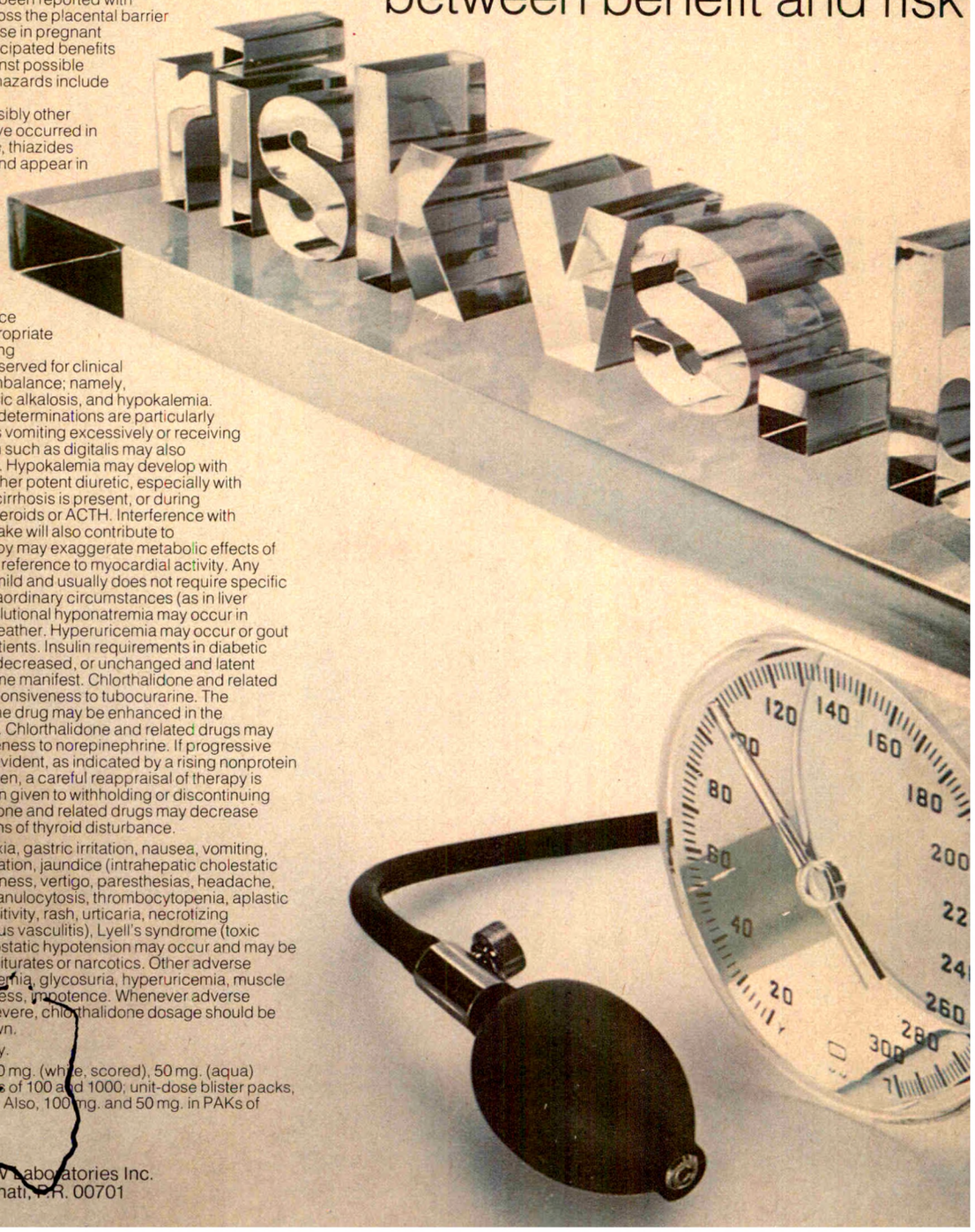
This study of 28 patients with proved pericardial effusion demonstrates the ability of wide angle two dimensional echocardiography to identify accurately intracardiac and pericardial anatomy and to reduce the pitfalls inherent in the diagnosis of percardial effusion. In all six patients with a small pericardial effusion, the fluid appeared to be totally posterior at the diaphragmatic portion of the atrioventricular groove or apical to it. Although moderate-sized effusions retained this prominent posterior localization, there was a more even distribution of the pericardial fluid anteriorly, apically and laterally. In patients with a large pericardial effusion, the posteromedial and apical recesses of the pericardial sac contained a disproportionate amount of fluid compared with the space behind the posterobasal left ventricular myocardium. These findings of the volume distribution of various-sized pericardial effusions suggest that single dimensional M mode quantification is most accurate for moderate-sized effusions and less valid for small and large pericardial effusions.

Continued on page A15

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 30 tablets, boxes of 6.

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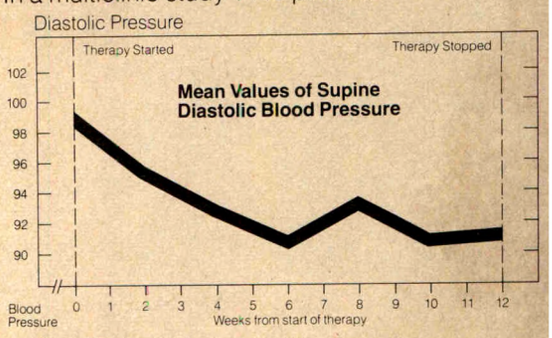
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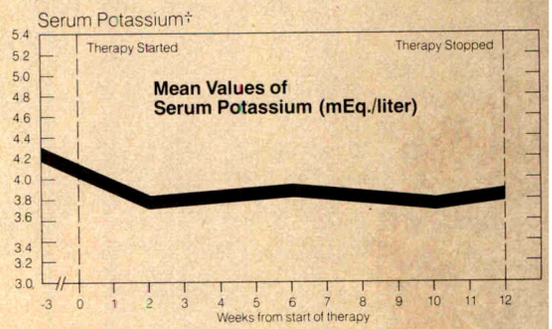
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*Multiclinic study involved 112 patients in: New Orleans, LA; Denver, CO; Nassau, Bahamas; Madison, WI; Paterson, NJ; East Meadow, NY. Data on file, USV Laboratories Inc.

†With thiazide and thiazide-like diuretics, it is possible to develop certain electrolyte imbalances including hypokalemia, hyperuricemia and hyperglycemia.

In a multiclinic study*: 112 patients

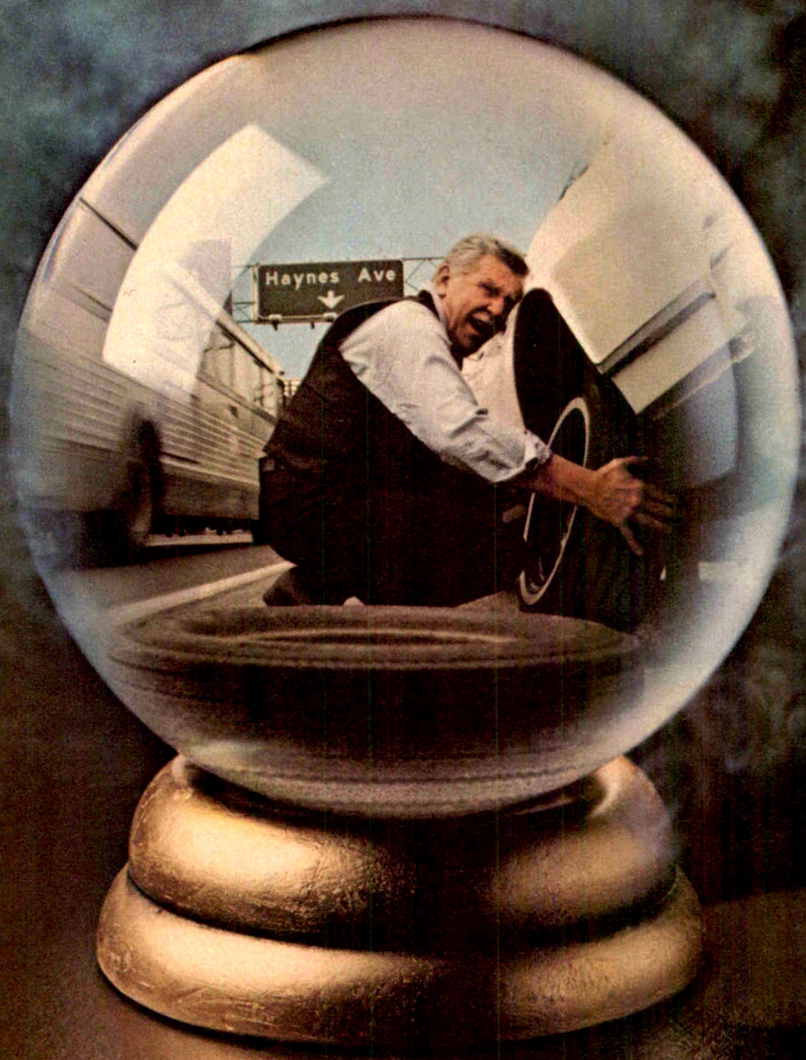






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SUMMARY OF PRESCRIBING INFORMATION

Indications: Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

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CONTENTS

913 Ventricular Fibrillation During Programmed Ventricular Stimulation: Incidence and Clinical Implications

SCOTT R. SPIELMAN, ARDESHIR FARSHIDI, LEONARD N. HOROWITZ and MARK E. JOSEPHSON

Programmed ventricular stimulation, a widely used technique for evaluating properties of ventricular conduction, tachycardias and other electrophysiologic effects, caused ventricular fibrillation in 3.3 percent of 300 consecutive patients studied with this method. This complication occurred only in response to double ventricular extrastimuli in patients in whom spontaneous episodes were more likely to occur. All 10 patients with ventricular fibrillation during programmed stimulation had suspected or documented ventricular tachycardia or fibrillation. In this study no morbidity beyond that of electrical defibrillation was associated with the induction of ventricular fibrillation. These data demonstrate (1) ventricular extrastimulation can be performed with safety in patients who are in clinically stable condition; (2) single extrastimuli delivered during sinus rhythm, ventricular pacing or ventricular tachycardia do not induce ventricular fibrillation; and (3) the initiation of ventricular fibrillation in the laboratory may be predictive of its spontaneous occurrence.

919 Value of a Noninvasively Induced Ventricular Extrasystole During the Echocardiographic and Phonocardiographic Assessment of Patients With Idiopathic Hypertrophic Subaortic Stenosis

GERALD H. ANGOFF, DANIEL WISTRAN, LAURENCE J. SLOSS, JOHN E. MARKIS, PATRICIA C. COME, PAUL M. ZOLL and PETER F. COHN

The mechanically induced extrasystole, as shown in 15 patients with idiopathic hypertrophic subaortic stenosis, is a valuable addition to the noninvasive methods available for the diagnosis and long-term evaluation of patients with this anomaly. Nine of the 15 patients showed ventricular obstruction in the beat after the ventricular extrasystole. All nine had greater than 20 msec prolongation of uncorrected systolic ejection time in the postextrasystolic beat of the carotid pulse tracing. Of the six patients subjected to cardiac catheterization, three patients without ventricular obstruction after a noninvasively induced ventricular extrasystole had no obstruction, and three patients who did have such obstruction also demonstrated obstruction at rest or after provocative maneuvers during catheterization. This method, alone or in addition to provocation with the Valsalva maneuver and amyl nitrite inhalation, allows easily repeated characterization of the labile hemodynamic state of this disorder.

925 Effectiveness of Increasing Hours of Continuous Ambulatory Electrocardiography in Detecting Maximal Ventricular Ectopy. Continuous 48 Hour Study of Patients With Coronary Heart Disease and Normal Subjects

HAROLD L. KENNEDY, VIJAY CHANDRA, KARIN L. SAYTHER and DENNIS G. CARALIS

This clinical study of consecutive 24 hour recordings demonstrates that increasing the length of ambulatory Holter monitoring reveals more severe types and greater frequencies of ventricular ectopy. Ambulatory recordings of less than 24 hours' duration underdetect the maximal ventricular ectopy of patients with coronary heart disease, particularly in defining complex grades or high frequency rates. Examination of the initial hour of study or an hour of dynamic activity frequently failed to disclose maximal ventricular ectopy. Most patients are asymptomatic during their maximal ventricular ectopy. These results support the use of initial 24 hour ambulatory electrocardiographic examination of patients with coronary heart disease and suggest that a continuous 36 hour recording may be more appropriate to detect maximal ventricular ectopy in some patients at high risk for serious ventricular arrhythmias.

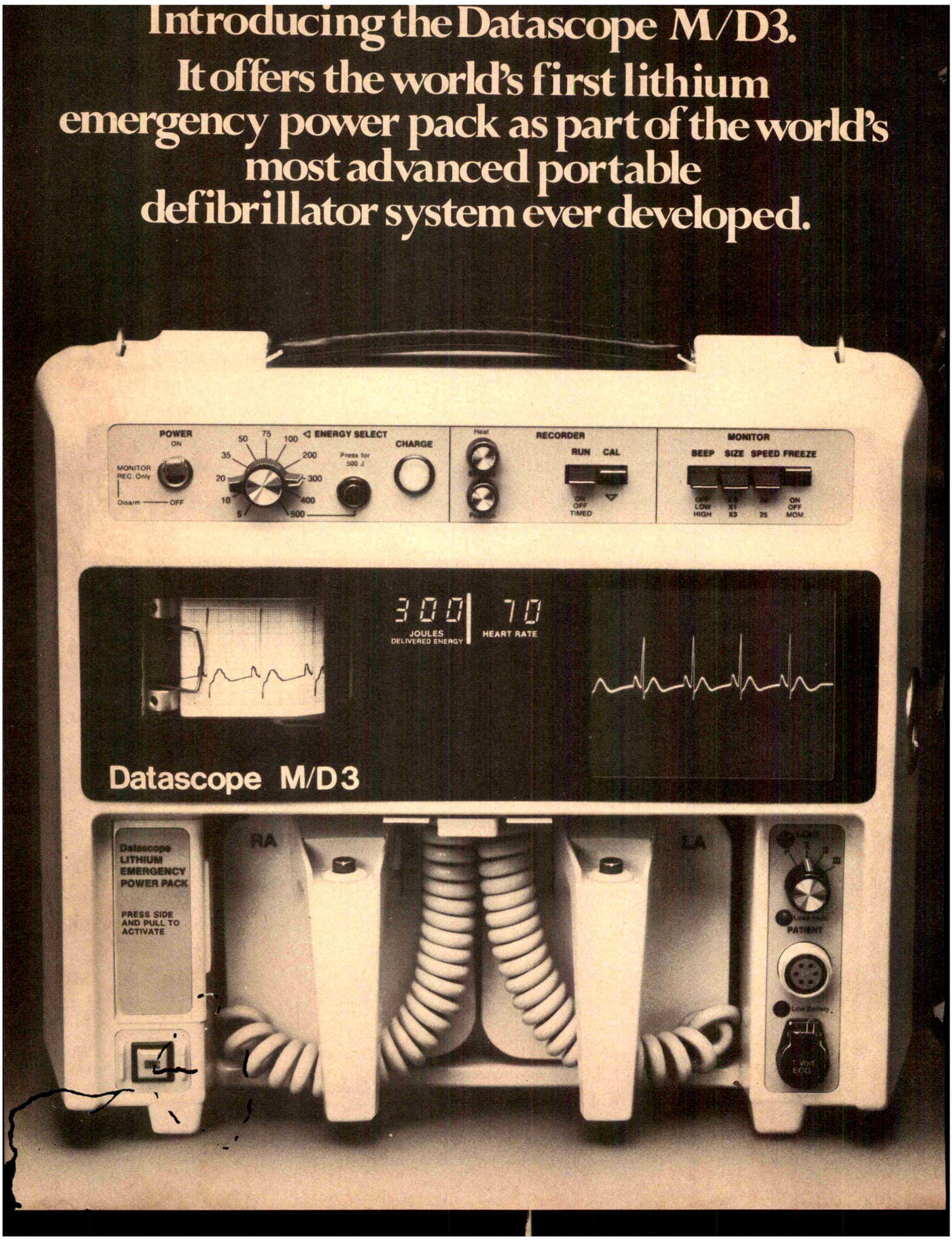
931 Effects of Digitalis on Ventricular Myocardial and His-Purkinje Refractoriness and Reentry in Man

JOSEPH ANTHONY C. GOMES, MALKIAT S. DHATT, MASOOD AKHTAR, CLARITA R. CARAMBAS, DAVID S. RUBENSON and ANTHONY N. DAMATO

Using the ventricular extrastimulus (V_2) technique in 17 patients, these studies show that in the intact human heart digitalis significantly decreased ventricular myocardial refractoriness, did not significantly affect retrograde conduction and refractoriness of the His-Purkinje system and widened the zone of reentry within the His-Purkinje system. These observations suggest that digitalis has the propensity of sustaining reentry over a larger range of premature ventricular depolarizations. The effects of ouabain on reentry within the His-Purkinje system

Continued on page A18

Introducing the Datascope M/D3. It offers the world's first lithium emergency power pack as part of the world's most advanced portable defibrillator system ever developed.



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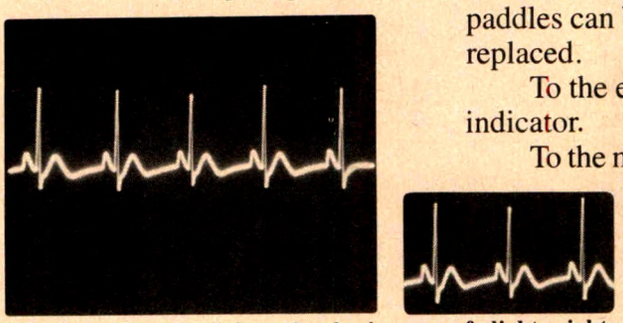
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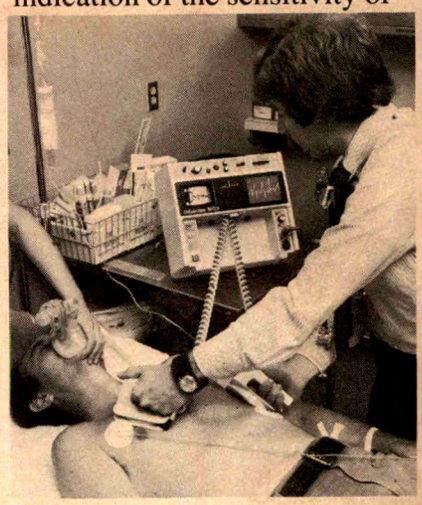
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To the document switch on the paddles which triggers the strip chart recorder. To the convenient way in which the paddles can be removed and replaced.

To the electrode lead fault indicator.

To the manner in which the battery pack can be rapidly ejected for replacement.

To the fact that batteries are recharged in less than 5 hours instead of the usual 16.

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The Datascope M/D3 Defibrillator System

CONTENTS

were related to the disparity in refractoriness between ventricular myocardium and the His-Purkinje system. Because most of these subjects had a normal heart and retrograde studies were performed at constant paced heart rates, it is difficult to make broad application of the data to the clinical setting of patients with a diseased heart in sinus rhythm or atrioventricular block with long-term exposure to the therapeutic or toxic effects of the glycoside.

EXPERIMENTAL STUDIES

939 **Electrograms From the Canine Sinoatrial Pacemaker Recorded in Vitro and in Situ**

MARVIN CRAMER, ROBERT J. HARIMAN, ROBERT BOXER and BRIAN F. HOFFMAN

Evidence is presented that the canine sinus node gives rise to characteristic extracell potentials that can be recorded through appropriate leads. These potentials, produced by membrane currents of sinus pacemaker cells, provide an extracell electrogram truly representative of electrical activity of the sinus pacemaker. These results suggest that the human sinus node is also very likely to produce specific extracell potentials that can be recorded by minor modifications of currently existing techniques. In fact, the investigators have already applied their technique to the recording of sinus nodal electrograms during cardiac catheterization in 26 patients.

947 **Acute Coronary Occlusion in the Pig: Effect of Nitroglycerin on Regional Myocardial Blood Flow**

ALBERT S. MOST, DAVID O. WILLIAMS and RONALD W. MILLARD

The pig heart, unlike that of the dog, lacks appreciable preformed collateral vessels but has an anastomotic subendocardial network similar to that described in man. It permits the study of changes in ischemic zone blood flow after abrupt coronary occlusion, as may occur in a significant subset of patients. Hemodynamic data in 10 closed chest, anesthetized pigs after an acute balloon catheter occlusion of the left anterior descending coronary artery showed no significant changes in arterial pressure, left atrial pressure or cardiac output. Nitroglycerin reduced arterial systolic pressure and significantly increased the heart rate. The endocardial/epicardial flow ratio in the normal zone decreased slightly with nitroglycerin and returned to the control level after the addition of phenylephrine. These data also indicate that the myocardial infarct zone in the pig contains a core of severely ischemic muscle that may not be amenable to pharmacologic influence. The pig's postocclusion myocardial blood flow pattern is influenced far less by systematically infused nitroglycerin with or without an alpha adrenergic agonist.

954 **Two and Three Dimensional Display of Myocardial Ischemic "Border Zone" in Dogs**

ALDEN H. HARKEN, CLYDE H. BARLOW, WESLEY R. HARDEN, III and BRITTON CHANCE

Utilizing a special fluorophotographic method that permits high resolution two dimensional evaluation of epicardial and myocardial oxidation-reduction states, these investigators were able to delineate the intramyocardial ischemic border of the dog myocardium in two ways after ligation of a diagonal branch of the left anterior descending coronary artery: (1) The distance between nicotinamide adenine dinucleotide-fluorescent ischemic cells and adjacent nonfluorescent cells was less than 0.1 mm; (2) the distance between homogeneously NADH-fluorescent tissue and homogeneously nonfluorescent tissue (across the zone of island normoxia) may be as wide as 6 to 8 mm.

960 **Superiority of Practolol Versus Propranolol in Protection Against Ventricular Fibrillation Induced by Coronary Occlusion**

DAVID L. PEARLE, DANIEL WILLIFORD and RICHARD A. GILLIS

In this study practolol, in contrast to no treatment or treatment with propranolol, afforded significant protection against ventricular fibrillation in dogs subjected to ligation of the left anterior descending and first septal coronary arteries. Ventricular fibrillation developed in only one of seven dogs pretreated with practolol, in six of seven dogs in the control group and in six of seven dogs treated with propranolol. Despite these results, practolol is unlikely to be approved for use in human beings because of adverse effects, including sclerosing peritonitis, cutaneous and ocular reactions and a lupus erythematosus-like syndrome. The demonstrated difference between the cardioselective beta adrenergic receptor blocking agent practolol and the noncardioselective agent propranolol suggests that cardioselectivity may be a critical factor, although other differences between these agents such as the degree of intrinsic sympathetic agonist activity may also be important.

Continued on page A20



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METHODS

965 **Comparative Study of Two Methods of Estimating Sinoatrial Conduction Time in Man**

GÜNTER BREITHARDT and LUDGER SEIPEL

Comparison of the programmed premature atrial stimulation technique with a new approach using continuous atrial pacing just above the spontaneous cycle length in 23 patients suggests that data from these two techniques cannot be easily compared and that premature atrial stimulation may depress sinus nodal automaticity more than continuous atrial pacing. The observed differences in results may also be due to a more pronounced delay of retrograde conduction during premature atrial stimulation than during continuous atrial pacing. The continuous pacing technique, if found valid, will permit all catheterization laboratories to measure sinoatrial conduction time because no special stimulator is needed.

PEDIATRIC CARDIOLOGY

973 **Right Atrial Ultrastructure in Congenital Heart Disease. I. Comparison of Ventricular Septal Defect and Endocardial Cushion Defect**

TUAN DUC PHAM, ANDREW L. WIT, ALLAN J. HORDOF, JAMES R. MALM and JOHN J. FENOGLIO, Jr.

Ultrastructural studies of the operatively resected right atrium from six patients with a ventricular septal defect, normal right atrial mean pressure and no right atrial volume overload showed normal atrial muscle cells measuring 6 to 12 μ in diameter. Similar studies in six patients with an endocardial cushion defect, elevated right atrial mean pressure and right atrial volume overload showed atrial muscle cells that were generally larger than 12 μ in diameter, irregular and multiple and occasionally widened intercalated discs and other degenerative changes. These ultrastructural changes suggest that hypertrophy of the right atrium may be secondary to volume overload of the atrium whereas degenerative changes may be secondary to increased right atrial pressure. The changes in cell ultrastructure that result from increased atrial volume and pressure in patients with an endocardial cushion defect may not be reversed, and functional abnormalities may persist after surgical correction.

983 **Electrophysiologic Studies in Tricuspid Atresia**

MARIA SERRATTO and DEVKISHIN B. PAHLAJANI

Electrophysiologic and His bundle studies in five patients with tricuspid atresia disclosed prolonged intraatrial conduction time caused by a hypertrophied and dilated right atrium with increased internodal distance due to stretching of internodal pathways. The A-H interval was normal in all; the H-V interval was short in three and normal in two. These data support the view that the abnormal left axis deviation and counterclockwise QRS forces in tricuspid atresia are due to the early activation of the posteroinferior part of the left ventricle, which in turn is related to the abnormal course of the left bundle and early origin of its posterior branches. The refractory periods were also normal, suggesting functional integrity of conduction through the atrioventricular node and bundle branches.

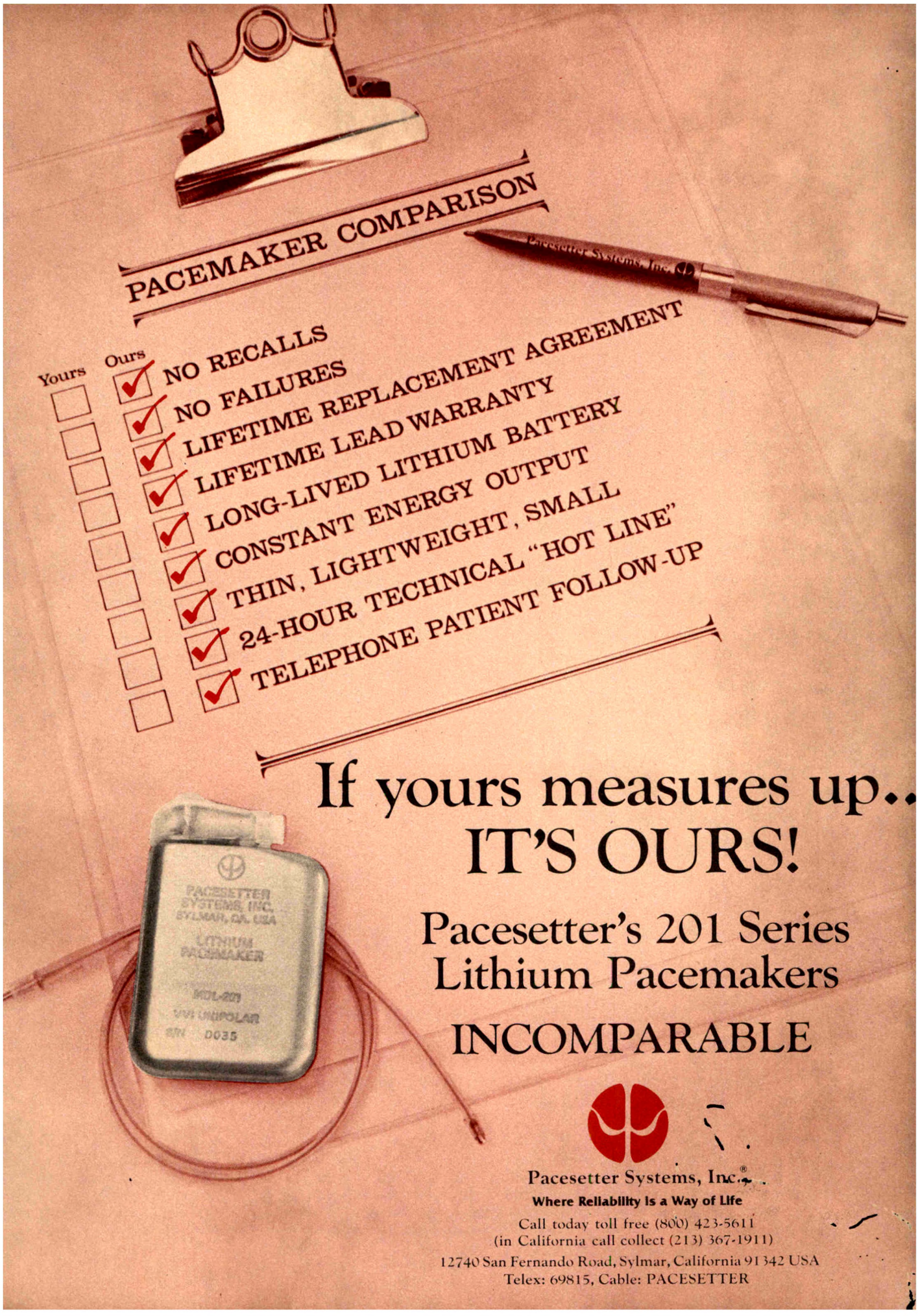
STUDIES IN HYPERTENSION

987 **Systemic and Pulmonary Hemodynamic Effects of Saralasin Infusion in Hypertension. Predictability of Plasma Renin Status From Hemodynamic Changes**

SAKTI MOOKHERJEE, ANIS OBEID, ROBERT WARNER, GUNNAR ANDERSON, ROBERT EICH and HAROLD SMULYAN

Saralasin, a highly specific competitive analog of angiotensin II, decreases arterial pressure in subjects with angiotensinogenic hypertension and is useful as a screening test to detect the role of the renin-angiotensin system in the pathogenesis of hypertension. Hemodynamic measurements before and after 30 minutes of saralasin infusion in 26 fasting adults with hypertension showed a depressor response in 9, a nonresponse in 10 and an agonistic response with an increase in mean arterial pressure of greater than 10 mm Hg in 7. Additional data in this study show that saralasin infusion has complex hemodynamic effects on the cardiovascular system in hypertension that cannot be appreciated from the changes in arterial pressure alone.

Continued on page A22


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REPORTS ON THERAPY

993 Long-Term Medical Management of Hypertrophic Obstructive Cardiomyopathy

MARTIN J. FRANK, ABDULLA M. ABDULLA and MARIO I. CANEDO

Based on experience with 22 patients ranging in age from 15 to 61 years followed up for 110 patient years, these investigators conclude that "complete" beta adrenergic blockade supplemented by control of arrhythmia is optimal management for hypertrophic obstructive cardiomyopathy and that most patients do not require surgery. The average dose of propranolol required for maximal control of symptoms was 462 mg/day, and the most common unit dose was 120 mg before meals and at bedtime. In sharp contrast to the 14 percent average surgical mortality rate in such patients, none of the 22 patients in this study died during a mean follow-up period of 5 years while receiving an average dose of propranolol of 462 mg/day. Improved diastolic compliance after propranolol therapy may be responsible for the decrease in signs of congestive failure and dyspnea and for the prevention of atrial fibrillation in these patients. The only clear-cut indication for surgical myotomy-myectomy is clinical deterioration in a patient with persistent severe outflow obstruction documented at recatheterization after aggressive prolonged medical management.

002 Prolongation of Cardiac Conduction Times by Intravenous Aprindine in Man

H. LEON GREENE, PHILIP R. REID and ALLEN H. SCHAEFFER

Intravenously injected aprindine in 48 patients with refractory ventricular or supraventricular arrhythmias prolonged conduction transiently in the atria, the atrioventricular (A-V) node, the His-Purkinje system and the ventricles. The refractory times of the atria, A-V node and ventricles increased insignificantly. A-V block did not develop, and side effects were minor. This study demonstrated more profound effects on conduction than previous intravenous aprindine studies. Although aprindine is not absolutely contraindicated in patients with bundle branch or A-V block and refractory arrhythmias, it should be given carefully while monitoring the blood pressure and the QRS duration and A-V conduction in the surface electrocardiogram. Facilities should be available for emergency pacing in patients with conduction abnormalities before drug administration. The risks of side effects must be weighed against the seriousness and intractability of the arrhythmia.

007 Suppression of the Repetitive Ventricular Response: An Index of Long-Term Antiarrhythmic Effectiveness of Aprindine for Ventricular Tachycardia in Man

ALLEN H. SCHAEFFER, H. LEON GREENE and PHILIP R. REID

In this study 23 of 27 patients (85 percent) with refractory ventricular tachycardia had a repetitive ventricular response before the infusion of aprindine; only 6 patients (22 percent) had this response after the infusion. Over a mean evaluation period of 12 ± 7.3 months, 21 (78 percent) of the total group had a good clinical response to aprindine. Twenty of the 21 patients who had no repetitive response after intravenous aprindine had a good clinical response to oral aprindine compared with only 1 of the 6 patients in whom the repetitive ventricular response remained. This study demonstrates the usefulness of the electrophysiologic evaluation for the repetitive ventricular response and the value of acute suppression of this response by aprindine as predictive of clinical responsiveness to long-term oral administration of aprindine.

013 Unilateral Stellate Block in the Treatment of Hypertension After Coronary Bypass Surgery. Implications of a New Therapeutic Approach

ROBERT C. TARAZI, F. GEORGE ESTAFANOUS and FETNAT M. FOUAD

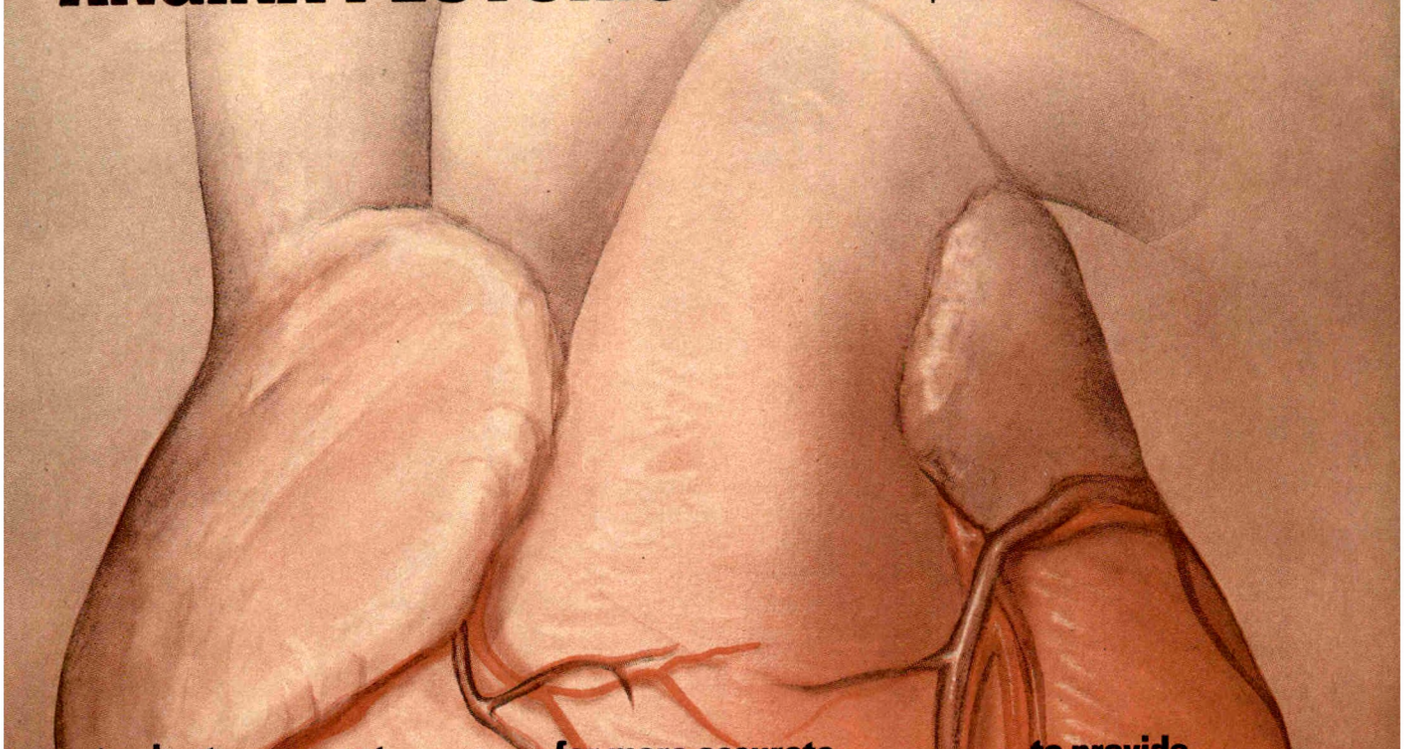
Right or left unilateral stellate ganglion blockade effectively controlled hypertension immediately after myocardial revascularization in 18 of 27 patients, mainly by interrupting the afferent limb of a pressor reflex. Cardiac output was unaltered; control of the hypertensive crisis was associated with a significant reduction in total peripheral resistance, irrespective of the side infiltrated. These and other data suggest that reflexes originating from the heart or great vessels may play an active role in cardiogenic hypertension and that unilateral stellate ganglion blockade may control it.

Continued on page A24

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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REVIEWS

1019 **"Variant" Angina: One Aspect of a Continuous Spectrum of Vasospastic Myocardial Ischemia. Pathogenetic Mechanisms, Estimated Incidence, Clinical and Coronary Arteriographic Findings in 138 Patients**

ATTILIO MASERI, SILVA SEVERI, MAURIZIO DE NES, ANTONIO L'ABBATE, SERGIO CHIERCHIA, MARIO MARZILLI, ANNA MARIA BALLESTRA, OBERDAN PARODI, ANDREA BIAGINI and ALESSANDRO DISTANTE

This comprehensive study of the characteristic features of 138 patients with "variant" angina concludes that this form of angina represents only one aspect of a continuous spectrum of vasospastic acute myocardial ischemia observable in any phase of ischemic heart disease and in the presence of a variable degree of coronary atherosclerosis. Anginal attacks at rest with S-T segment elevation or depression were not preceded by any increase of the hemodynamic determinants of myocardial oxygen consumption. Pain was always a late phenomenon relative to the onset of ischemia and may even be absent. The intensity and extension of vasospasm and degree of collateral perfusion may result in various degrees and different transmural distributions of myocardial ischemia. The data demonstrate that elevation of the S-T segment represents the most dramatic and striking electrocardiographic change characteristic of vasospastic angina rather than its only electrocardiographic manifestation. Coronary vasospasm may be one of the initiating causes of myocardial infarction or acute myocardial ischemia, producing life-threatening arrhythmias or death. Treatment remains empirical and symptomatic.

1036 **The Pericardium: An Essay on Some Recent Developments**

RALPH SHABETAI

Detailing the importance of pericardial function, this comprehensive review indicates that the pericardium exerts an important restraining influence on the left ventricle, modifies the response of the left ventricle to altered preload and plays a major role in the dynamic interaction between the ventricles. In patients with intrinsically elevated left ventricular diastolic pressure, cardiac tamponade causes equilibration between right (but not left) ventricular diastolic pressure and pericardial pressure. Effusive-constrictive pericarditis is common in neoplastic involvement of the heart and pericardium. Still to be settled are the relative value and use of dialysis, intrapericardial corticosteroids, pericardiocentesis, surgical pericardial window and pericardiectomy in the management of various types of pericarditis.

DIAGNOSTIC SHELF

1044 **Demonstration of the Mechanism by Which Mitral Regurgitation Mimics Aortic Stenosis**

ELLIOTT M. ANTMAN, GERALD H. ANGOFF and LAURENCE J. SLOSS

In this 68 year old man with ruptured chordae tendineae of the posterior mitral leaflet, the murmur of mitral regurgitation clinically mimicked aortic stenosis. Echocardiographic and angiographic evidence confirmed the hypothesis that acoustic energy derived from a mitral regurgitant jet may be transmitted to the aorta by impingement of the jet upon the portion of the left atrial wall adjacent to the aortic root. At operation the papillary muscles and the aortic valve appeared normal. The mitral valve was replaced with a stented porcine aortic valve bioprosthesis.

CASE REPORTS

1049 **Atypical Ventricular Tachycardia as a Manifestation of Disopyramide Toxicity**

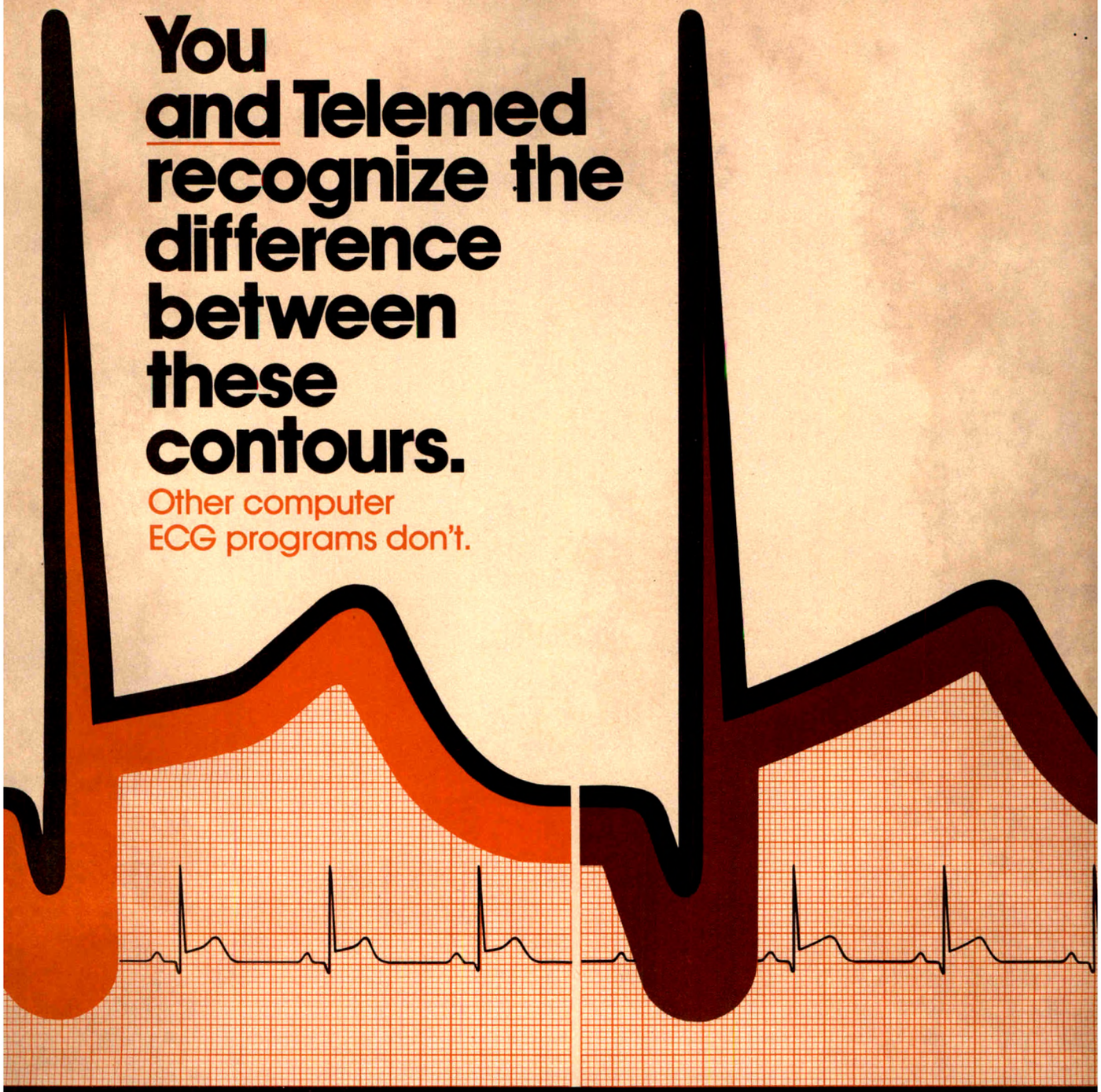
RICHARD S. MELTZER, EDWARD W. ROBERT, MAUREEN McMORROW and RANDOLPH P. MARTIN

Disopyramide, a type I antiarrhythmic drug with electrophysiologic properties similar to those of quinidine, caused an unusual ventricular tachyarrhythmia resembling the patient's previous rhythm but characterized by a slow rate and markedly widened QRS complexes simulating "torsade de pointes." Toxic plasma levels of disopyramide due to an inadvertent increase in dosage were documented when the atypical ventricular tachycardia was recorded.

Continued on page A26

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1054 **Torsade de Pointes: An Addition to the Nosography of Ventricular Tachycardia**
CHARLES E. KOSSMANN

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1057 **Letters to the Editor**

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Acute Myocardial Infarction With Normal Coronary Arteries—R. C. Pasternak, R. W. DeSanctis, S. D. Gertz, et al.

Ergonovine Maleate, Angina-Like Syndrome and Coronary Spasm—J. P. Liss, Jr. and F. A. Heupler, Jr.

Cardiac Rupture After Myocardial Infarction—G. M. FitzGibbon, G. D. Hooper, H. A. Heggtveit, et al.

Prognosis in Severe Unstable Angina Pectoris—R. A. Chahine, R. J. Luchi, H. W. Alison, et al.

Kussmaul's Sign in Pericardial Disease—D. H. Spodick and T. Mann

Application Site for Nitroglycerin Ointment—M. S. Hansen and P. W. Armstrong

Technique for Continuous Electrical Pacing During Pulse Generator Replacement—I. Bahadir, R. Koopot, E. B. Diethrich, et al.

1063 **American College of Cardiology News**

1067 **Books Received**

1068 **Author Index**

1071 **Subject Index**

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...hn Woden, M.D.
...mary Care Associates, Inc.
...edical Centre Plaza
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July 20, 1978

Harold Hoosier 58, M Record #5542

Dr. Woden:

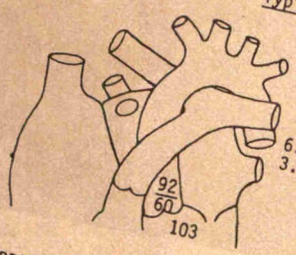
...you for referring Mr. Hoosier to our laboratory to be
...ed as a candidate for coronary surgery. Mr. Hoosier was

CARDIAC DIAGNOSTIC AFFILIATES
University Community Hospital

CARDIAC CATHETERIZATION REPORT A - Page 2

Name: Harold Hoosier 58, M Record #5542
Date: 7/20/78 Ht: 155cm Wt: 80kg BSA: 1.78m2

Typical Hemodynamics



	Sample Site	Pressure Data Normal	Phasic	Mean	HR	Note
LV	(mid)	140/12	87/1		72	1
LV	OFT	140/12	87/1			
AO	ASP	140/90	103/14			
			92/60	73	78	2

6.93L/min.
3.89L/min/m2

Note 1: Pre-angio with balloon off.
Note 2: Pullback, post-angio with balloon off.

CARDIAC DIAGNOSTIC AFFILIATES
University Community Hospital
56 Union Ave., Sudbury, Mass. 01776

Office: 617-443-9969
Hospital: 617-443-9886

CARDIAC CATHETERIZATION REPORT A

Name: Harold Hoosier 58, M Record #5542
Date: 7/20/78 Ht: 155cm Wt: 80kg BSA: 1.78m2

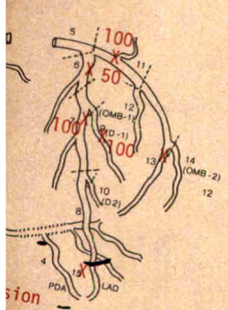
...eferring physician: John Woden, M.D.
...tending physician: Ward Halsom, M.D., Carol S. Perch, M.D.

...inical diagnosis: Pre-infarction angina / medical failure
...dication for study: Evaluate for coronary surgery

...cedure: Hemodynamics: Left heart, right femoral approach
Angiography: LV, RAO view. Coronaries via Judkins.
Other: Performed during balloon counterpulsation
Complications: None.

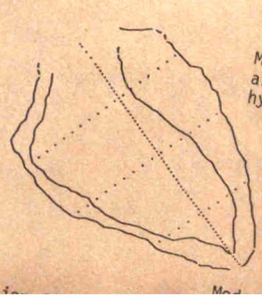
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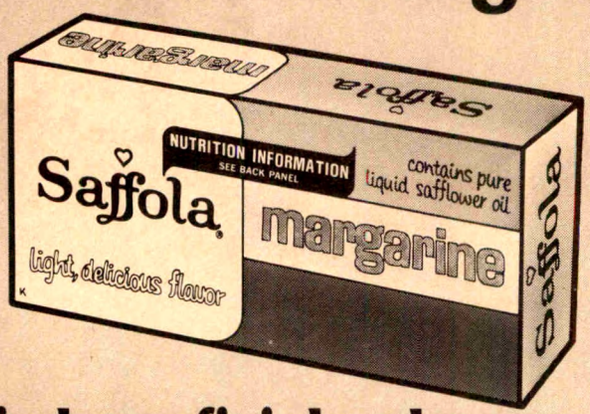
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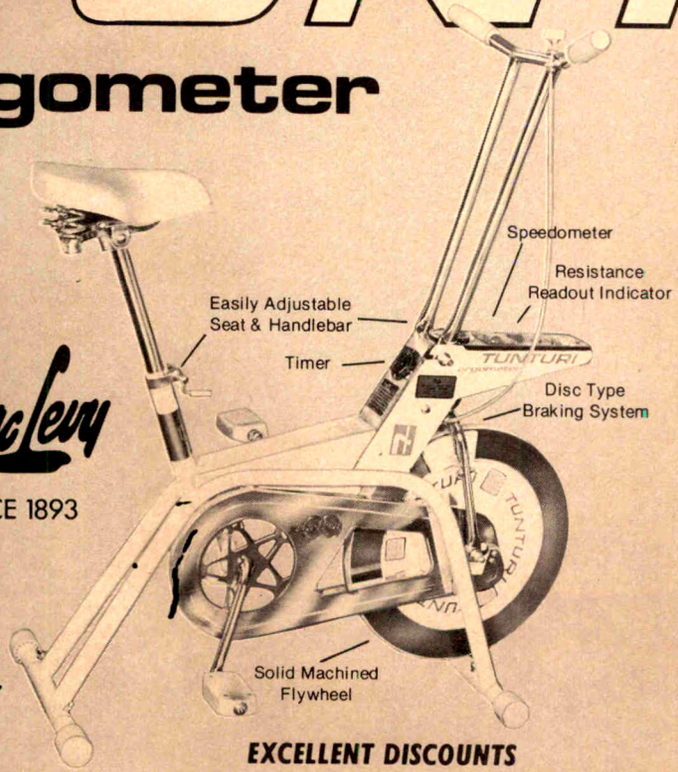
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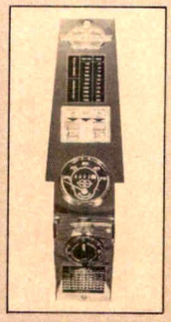
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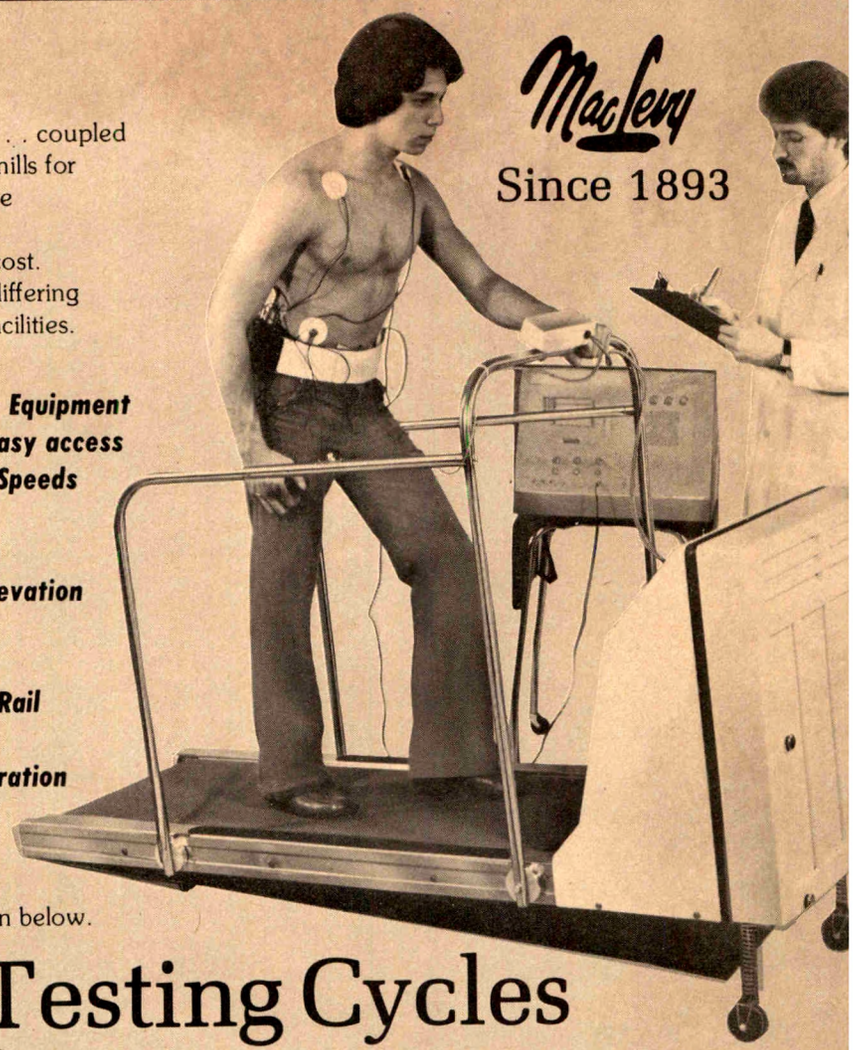
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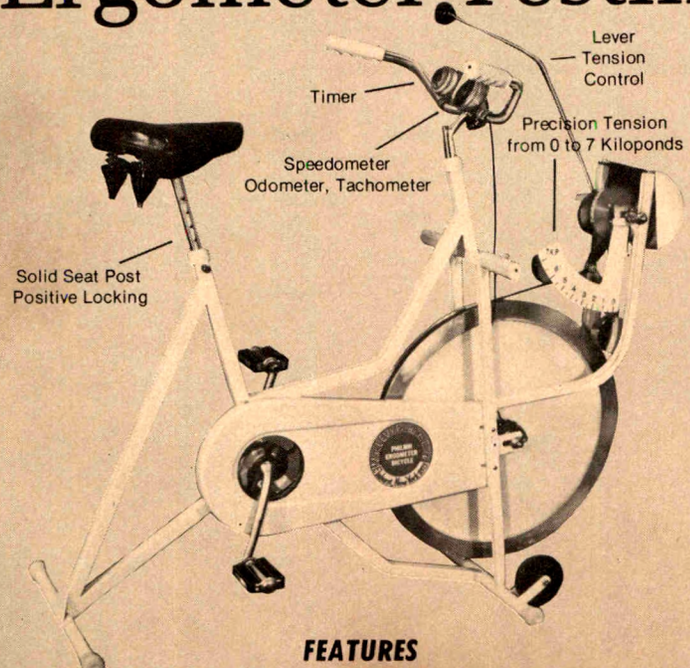


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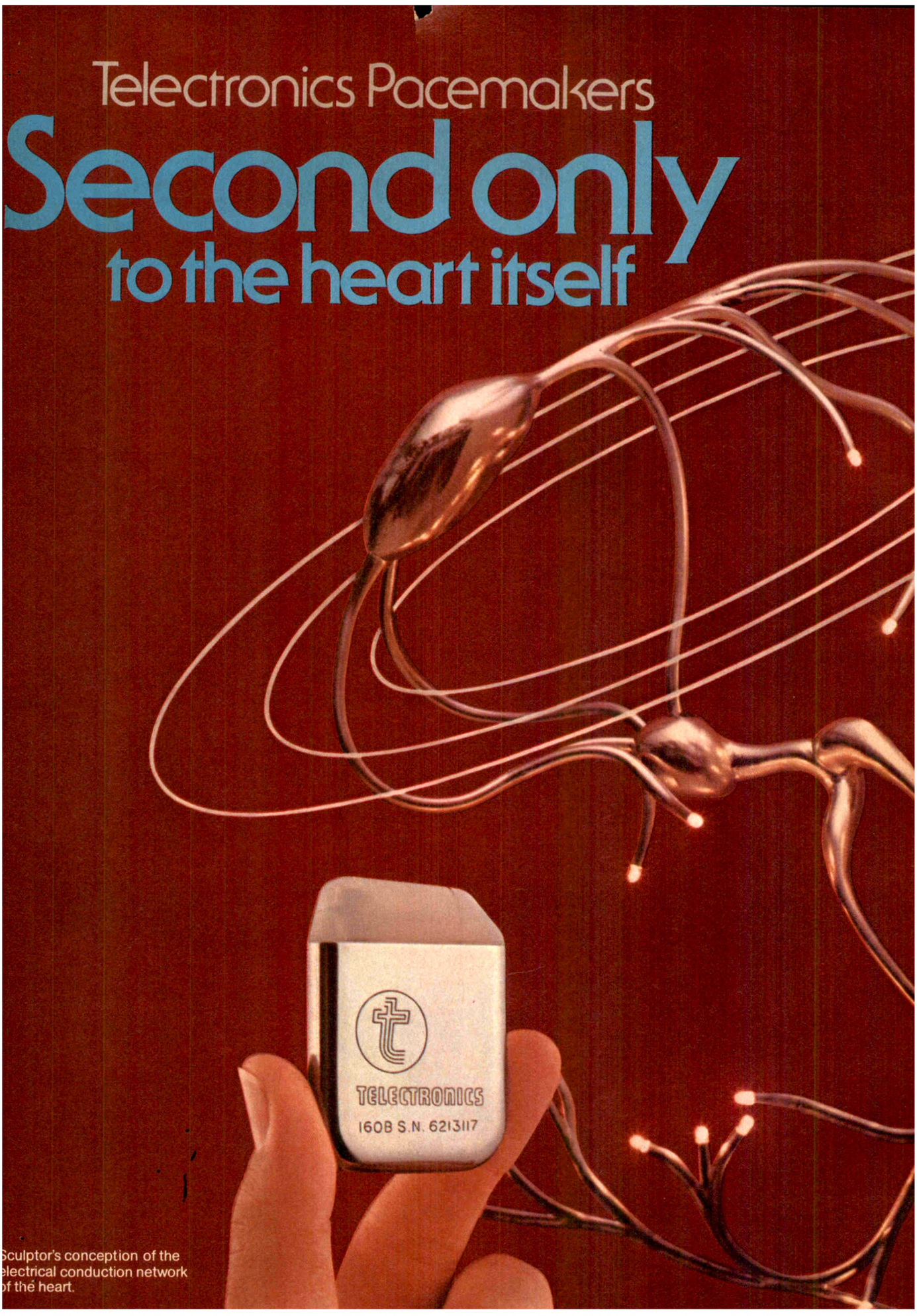
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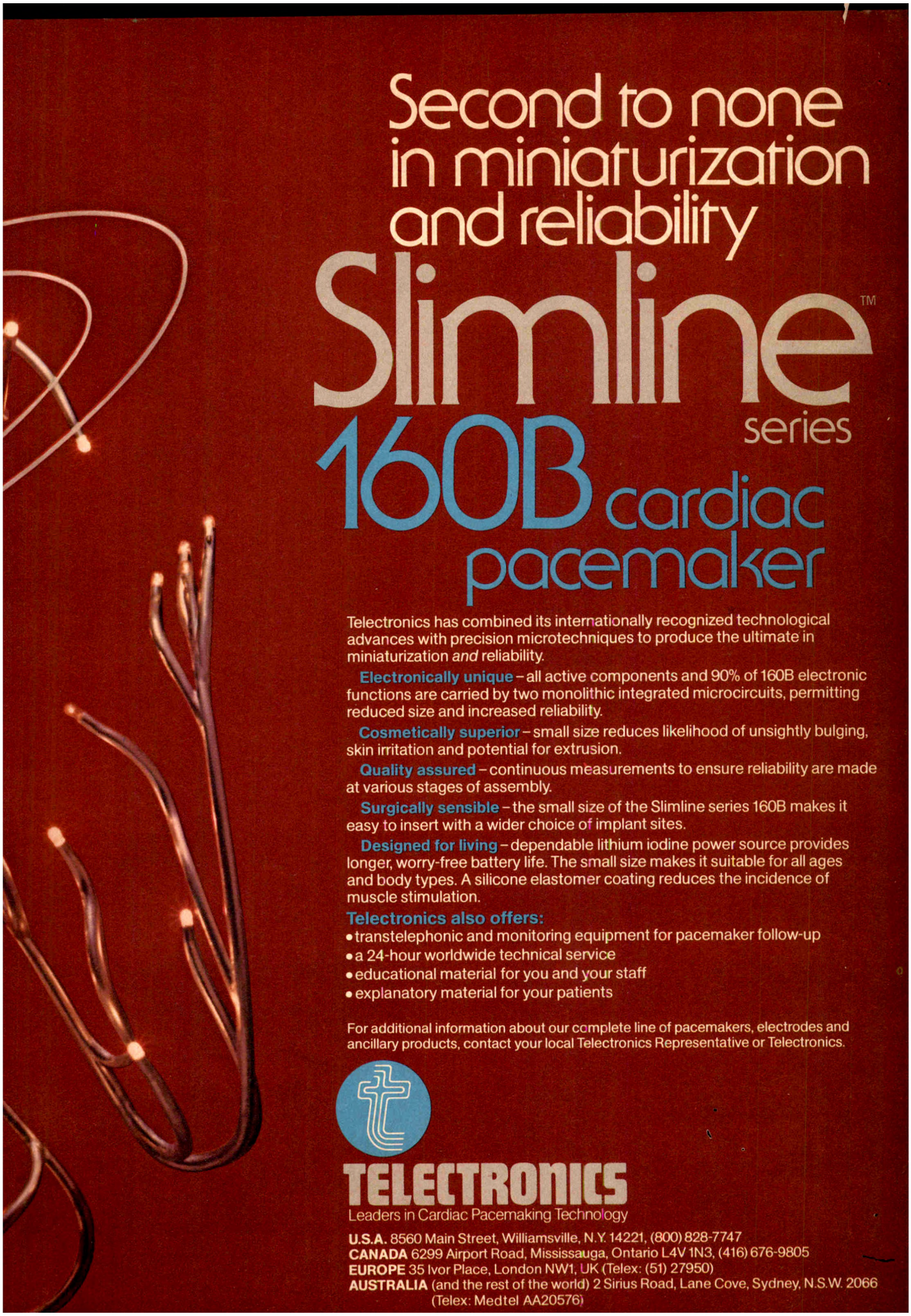
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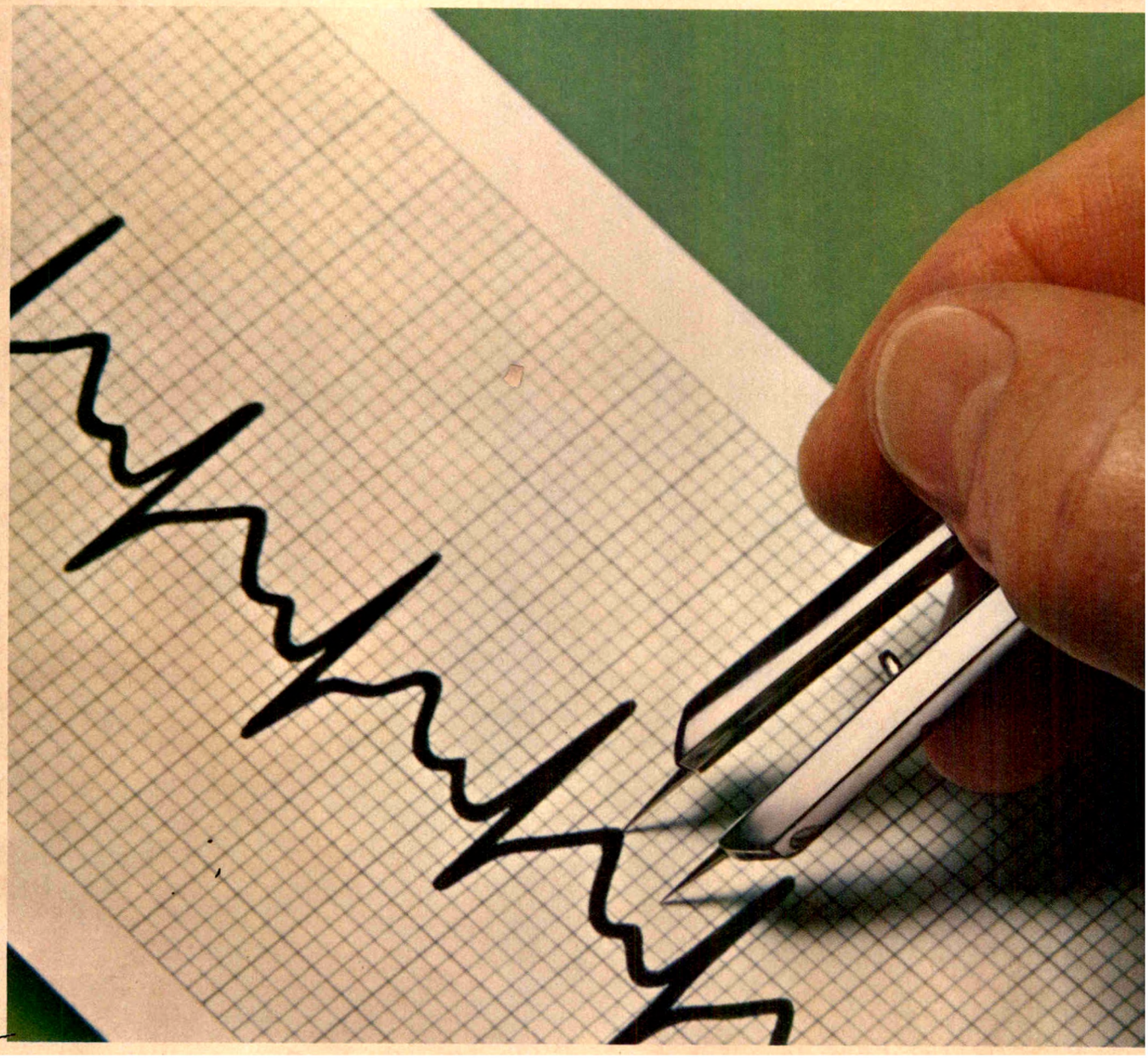
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INDERAL®
(propranolol hydrochloride)
PERFORMANCE IN CARDIAC ARRHYTHMIAS

EFFECTIVE ALONE OR IN COMBINATION



INDERAL (propranolol hydrochloride): Successful treatment of supraventricular arrhythmias for over 10 years

INDERAL, used alone or in combination with other antiarrhythmics, has improved or resolved a variety of supraventricular arrhythmias.[1-7]

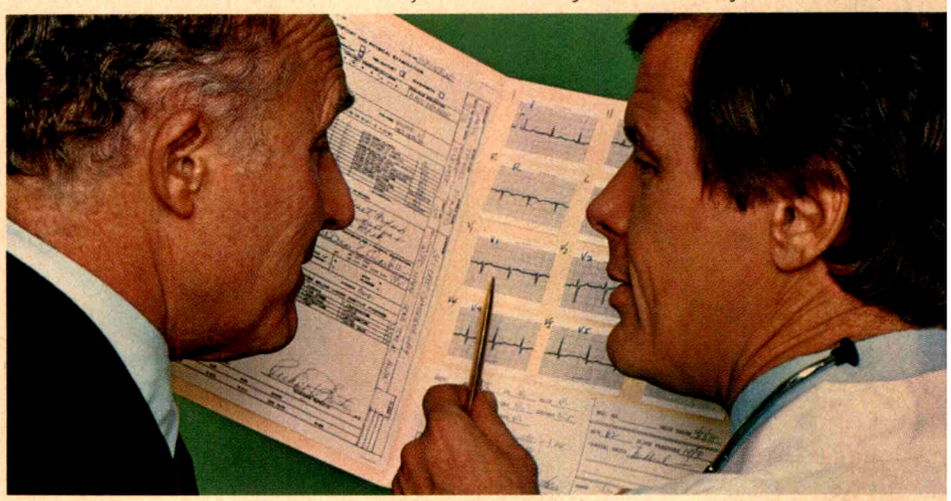
INDERAL alone: Results of use against atrial tachyarrhythmias in one series have recently been reported:

Arrhythmia	Patients	Proportion deriving benefit	
		Complete	Partial
Sinus tachycardia	86	59%	22%
Atrial tachycardia (including paroxysmal type)	154	61%	19%
Atrial flutter	50	54%	32%
Atrial fibrillation	139	53%	26%

Adapted from Coodley and Snyder.[1]

INDERAL is particularly effective in therapy of supraventricular tachyarrhythmias.[9] It slows depolarization of sinus and ectopic pacemaker cells, and retards impulse-conduction in the atria and across the AV node.[1,10,11] In cases where it cannot restore normal sinus rhythm, INDERAL is frequently effective in reducing the ventricular rate.[1-3,12-14] INDERAL may prevent recurrent supraventricular tachyarrhythmias when digitalis and quinidine fail to do so.[9,12] In addition, INDERAL is a useful short-term adjunct for arrhythmias of thyrotoxicosis, when





used with specific therapy. Since INDERAL may mask the clinical signs of hyperthyroidism, abrupt withdrawal should be avoided to prevent exacerbation of the symptoms of hyperthyroidism.

And in combination: INDERAL has also been used to complement the actions of other antiarrhythmic agents.[3-5,8,9,13] The combination of INDERAL and quinidine has suppressed supraventricular arrhythmias that have not responded to either drug alone.[3,9]

When toxic doses of digitalis glycosides occasionally fail to control the ventricular rate in patients with atrial fibrillation or flutter, addition of INDERAL to a digitalis glycoside, with reduction of the digitalis dosage, may prolong AV conduction to the point where satisfactory control of ventricular rhythm is established.[8,15]

INDERAL: Often effective in tachyarrhythmias of digitalis intoxication[2,9,10,14] INDERAL has been found useful in the treatment of certain digitalis-induced arrhythmias that persist following discontinuation of digitalis and correction of electrolyte disturbances, particularly hypokalemia. Its use in this setting may be limited by the presence of significant congestive failure or heart block, and the development of severe bradycardia. (Please see prescribing information on the next page for "Overdosage or Exaggerated Response.")

INDERAL is contraindicated in sinus bradycardia, greater than first degree heart block, and congestive heart failure unless the failure is secondary to tachyarrhythmias treatable with INDERAL. (See prescribing information for complete list of CONTRAINDICATIONS.)

Please see next page for prescribing information.

Ayerst

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

INDICATIONS: Cardiac Arrhythmias:

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.

May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL (propranolol hydrochloride) unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL (propranolol hydrochloride) is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE: At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS: Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.*, electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE:

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCES: 1. Shand, D.G.: N. Engl. J. Med. *293*:280 (Aug. 7) 1975. 2. Conn, R.D.: Postgrad. Med. *55*(No. 2):131 (Feb.) 1974. 3. Fors, W.J., Vanderank, C.R., and Reynolds, E.W.: Am. J. Cardiol. *27*:190 (Feb.) 1971. 4. Levi, G.F., and Proto, C.: Cardiology *55*:249, 1970. 5. Stern, S.: Am. Heart J. *74*(No. 2):170 (Aug.) 1967. 6. Luna, M.H., Adelson, E.I., and Miller, A.J.: Circulation *34*:767 (Nov.) 1966. 7. Gianelly, R.E., Griffin, J.R., and Harrison, D.C.: Ann. Intern. Med. *66*:667 (Apr.) 1967. 8. Coodley, E.L., and Snyder, S.: Am. Fam. Physician *14*(No. 5):146 (Nov.) 1976. 9. Miller, R.R., Amsterdam, E.A., and Mason, D.T.: Drug Therapy *5*:110 (Feb.) 1975. 10. Danahy, D.T., and Aronow, W.S.: Postgrad. Med. *61*(No. 1):113 (Jan.) 1977. 11. Gettes, L.S.: Med. Opinion *5*(No. 9):19 (Sept.) 1976. 12. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 13. Michaelson, S.P., and Wolfson, S.: Cardiovasc. Med. *1*(No. 3):213 (Nov.) 1976. 14. Wit, A.L., Hoffman, B.F., and Rosen, M.R.: Am. Heart J. *90*(No. 5):665 (Nov.) 1975. 15. Bigger, J.T., and Giardina, E.G.V.: Cardiovasc. Clin. *6*(No. 2):103, 1974.

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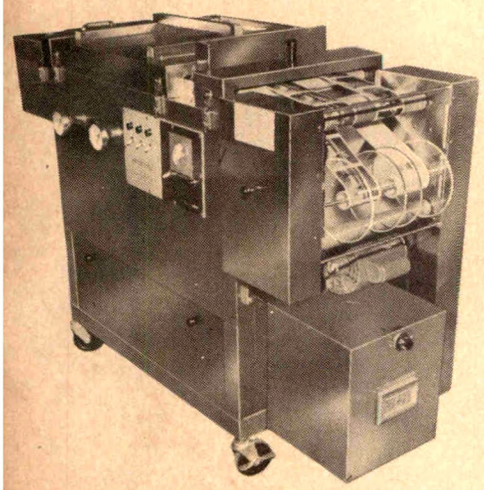
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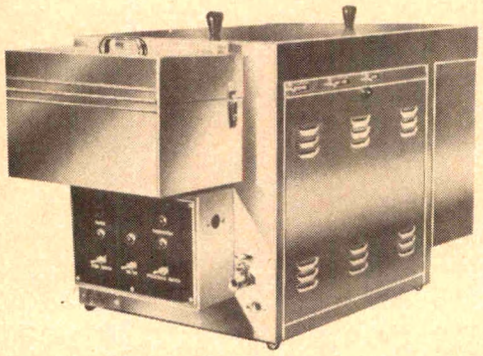
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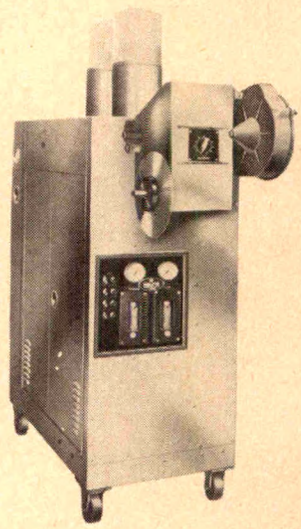
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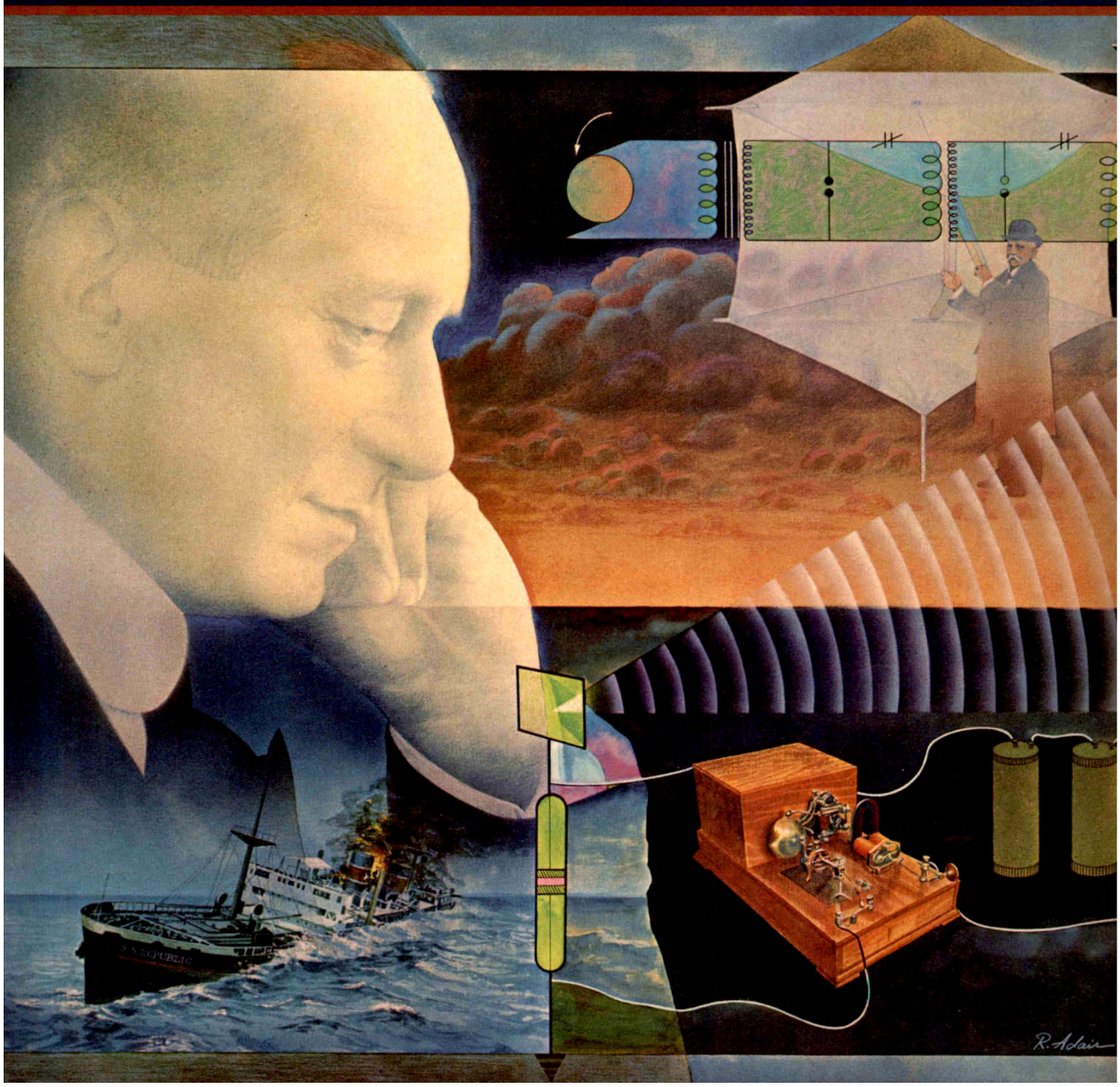
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Developing wireless technology, Marconi paved the way for the modern electronic achievement known as telemetry. Intermedics has applied this achievement to cardiac pacemaker technology. It is available in the CyberLith.

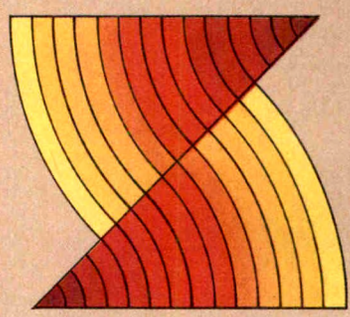


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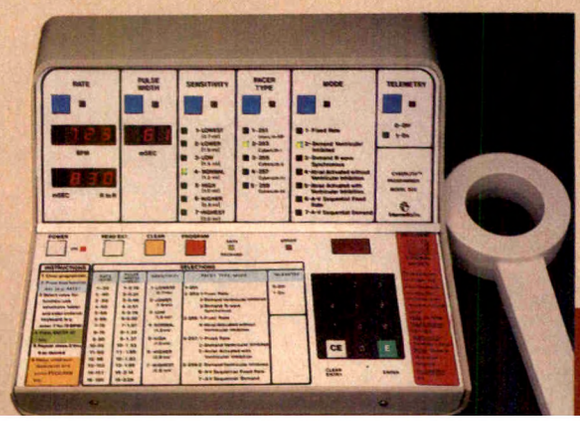
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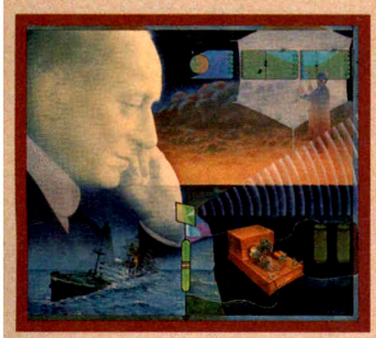
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Note:

The CyberLith is currently undergoing clinical evaluation and is not routinely available on a commercial basis.

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Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and relatively widely variable service life as a result of factors such as the initial capaci of the battery and the shelf storage time of the manufactured pacemak variations in electrode system resistances, stimulation rate, and the per centage of time the implanted pacemaker is inhibited; and random ele tronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or ele tromagnetic energy mimicking normal cardiac activity. In addition, ce tain environmental sources can couple sufficient energy into a pacema system to damage the pulse generator. Specifically, diathermy should n be used on pacemaker patients because of possible total inhibition of th pulse generator; electrocautery can inhibit and/or damage the pacema as well as cause burns or possible ventricular fibrillation; defibrillation c damage the pacemaker, and the presence of the pacemaker may cause creased cardiac muscle damage from defibrillation. Microwave ovens t do not exceed federal guidelines for leakage (0.5 mW/cm² at 2.5 cm fr the appliance) will not affect the pacemaker, but leakage in excess of th amount may cause interference. Certain electrical and gasoline-power appliances can cause inhibition of an implanted cardiac pacemaker system.

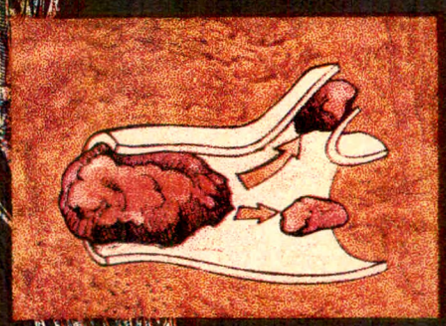
For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical metho for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, an cardiac tamponade have been reported.

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THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy–COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

*ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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March, 1977

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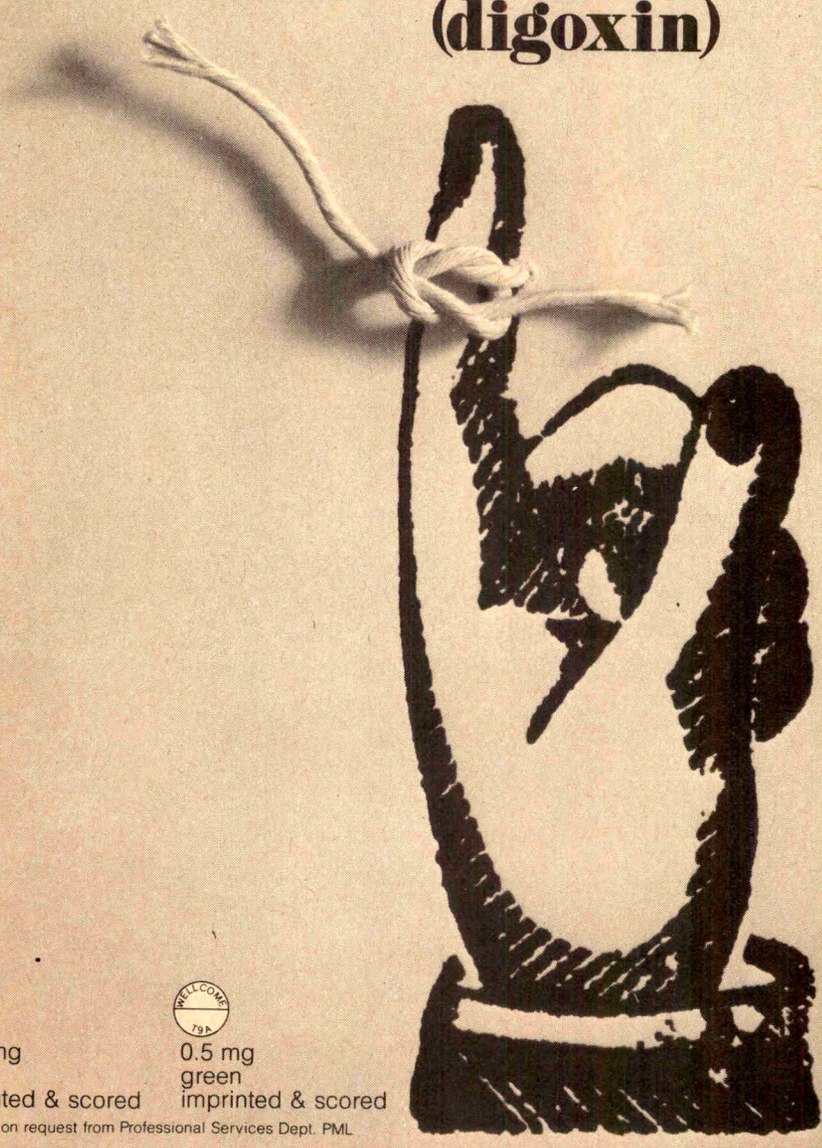
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VOLUME 4

NUMBER

CLINICAL STUDIES

Right Ventricular Infarction Complicating Left Ventricular Infarction Secondary to Coronary Heart Disease

Frequency, Location, Associated Findings and Significance From Analysis of 236 Necropsy Patients With Acute or Healed Myocardial Infarction

JEFFREY M. ISNER, MD, FACC
WILLIAM C. ROBERTS, MD, FACC

Bethesda, Maryland

Right ventricular infarction associated with left ventricular infarction wa identified by gross examination at necropsy in 33 (14 percent) of 23 patients with transmural myocardial infarction. Right ventricular infarctio occurred exclusively as a complication of posterior left ventricular in farction. Associated right ventricular infarction occurred in none of th 97 patients with isolated anterior wall infarction of the left ventricle, bu in 33 (24 percent) of the 139 patients with posterior left ventricular in farction. Transmural infarction of the posterior ventricular septum wa an additional prerequisite for right ventricular infarction. Of the 139 patien with infarction of the posterior left ventricular wall, 74 had no transmur infarction of the ventricular septum and none of these 74 had associate right ventricular infarction. In contrast, of the 65 patients with infarctio of the posterior left ventricular wall and transmural infarction of the ver tricular septum, 33 (50 percent) had associated right ventricular infar tion.

Among the 33 patients with right ventricular infarction, the infarct wa limited to the posterior right ventricular free wall in 27 (82 percent); the other 6 patients (18 percent) it extended to involve the anterolater right ventricular free wall. Among patients with a posterior left ventricul infarct, those with a right ventricular infarct had right ventricular dilatatio nearly three times ($P < 0.05$) more frequently than the patients witho a right ventricular infarct. Comparison of the same two groups disclose no differences in the patients' age, sex, extent of coronary arterial lumin narrowing, right ventricular hypertrophy, right ventricular thrombi or d ration of symptoms of myocardial ischemia.

Hemodynamic data in four patients with a right ventricular infarct di closed previously reported characteristic hemodynamics of right ve tricular infarction in only one patient. Recognition of right ventricular i farction is important because it implies specific therapy, namely, a gressive volume administration. Clinical evidence of *posterior left ve tricular infarction* and *right ventricular dilatation* should arouse stro suspicion of associated right ventricular infarction.

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received May 15, 1978; revised manuscript received July 11, 1978, accepted July 12, 1978.

Address for reprints: William C. Roberts, MD, Building 10A, Room 3E-30, National Institutes of Health, Bethesda, Maryland 20014.

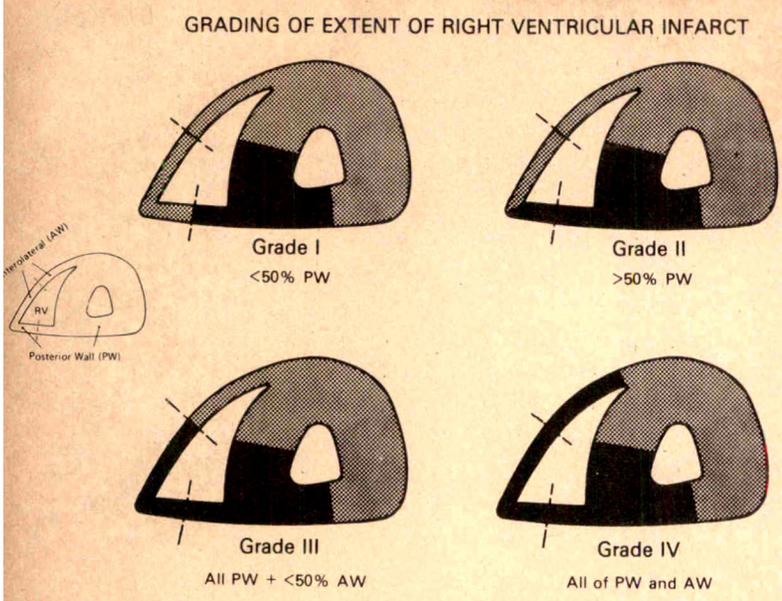
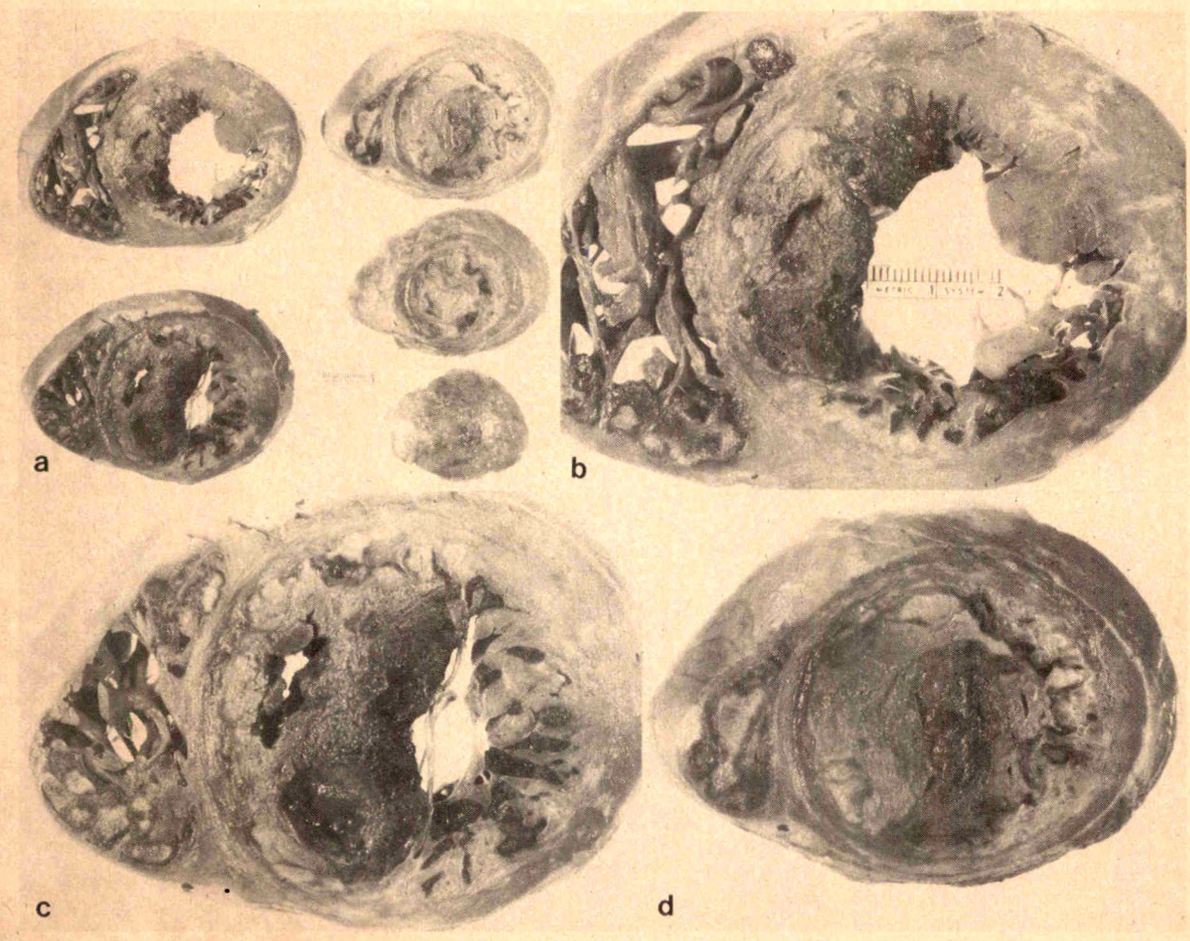


FIGURE 1. Diagram of transverse slices of cardiac ventricles illustrating the scheme used to grade the extent of the right ventricular (RV) infarct. The right ventricular infarct was classified as grade I when it involved less than 50 percent of the posterior wall (PW) of the right ventricle; grade II when it was limited to the posterior wall but involved more than 50 percent of it; grade III when it involved all of the posterior wall and some, but less than 50 percent, of its anterolateral wall (AW); and grade IV when it involved all of the right ventricular posterior wall and more than 50 percent of the anterolateral wall.



IGURE 2. Transverse slices of cardiac ventricles illustrating acute myocardial infarction of the right ventricular wall associated with infarction of he ventricular septum and the posterior and anterior walls of the left ventricle in a 66 year old man. The patient had the onset of typical clinical eatures of acute myocardial infarction beginning 25 days before death. The electrocardiogram showed changes consistent with an acute inferior vall myocardial infarct. Death occurred suddenly. **a,** transverse sections of the cardiac ventricles. **b,** close-up view of the upper left slice in **a,** showing hrombus in both ventricular cavities and necrosis of most of the septum. **c,** close-up view of the bottom left slice in **a,** showing necrosis of the ntire septum and all of the posterior right and left ventricular free walls. **d,** close-up view of the upper right slice in **a.** In this slice the infarct is circumferential.

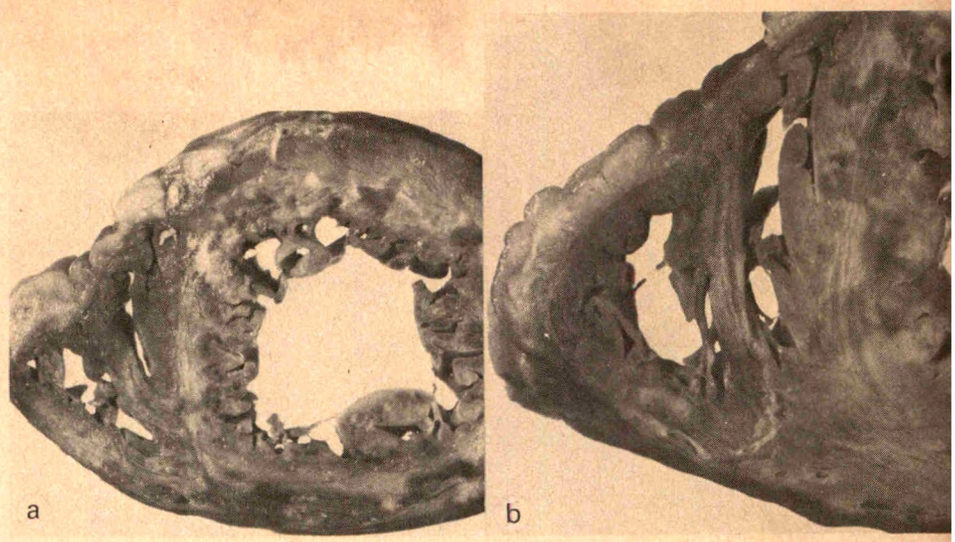


FIGURE 3. Patient 1 (Table IV). Acute right ventricular infarction associated with extensive necrosis of left ventricle in a 57 year old man who died 3 days after the onset of severe chest pain. The electrocardiogram showed changes of acute inferior myocardial infarction. The hemodynamic findings did not suggest associated right ventricular infarction. **a** and **b**, close-up views of two transverse slices of cardiac ventricles showing necrosis of the right ventricle that is limited to but involves more than 50 percent of the posterior wall (grade II). There is associated transmural necrosis of the ventricular septum.

TABLE I

Frequency of Right Ventricular Infarct Among Necropsy Patients With Transmural Left Ventricular Infarction and Relation to Involvement of Ventricular Septum

	Patients								
		Age (yr)		Sex				No	
LV Infarct	no.	Range	Aver-age	M	F	Transmural VS MI	RV MI	Transmural VS MI	RV MI
Anterior	97	26–90	69	67	30	68	0	29	0
Acute	60	26–90	74	36	24	43	0	17	0
Healed	37	31–80	60	31	6	25	0	12	0
Posterior	139	26–93	62	99	40	65	33 (51%)	64	0
Acute	56	38–93	64	37	19	32	16 (29%)	24	0
Healed	83	26–93	61	62	21	33	17 (20%)	50	0
Totals	236	26	65	166 (70%)	70 (30%)	133	33 (25%)	103	0

LV = left ventricular; MI = myocardial infarct; RV = right ventricular; VS = ventricular septal.

Myocardial infarction secondary to coronary arterial narrowing virtually always involves the left ventricular free wall and often also the ventricular septum. Involvement of the right ventricular free wall secondary to coronary luminal narrowing has until recently rarely been diagnosed clinically, and few morphologic studies have focused on its frequency or extent. The present study examines the frequency of right ventricular infarction in patients with associated transmural left ventricular infarction and determines its extent and relation to the site of the infarction of the left ventricle.

Patients Studied and Methods

All cases of acute or healed myocardial infarction accessioned in the Pathology Branch of the National Heart, Lung, and Blood Institute from January 1969 to February 1978 were reviewed. Patients with acute or healed myocardial infarction who had associated primary valvular heart disease, infiltrative myocardial disease or hypertrophic cardiomyopathy or who had cardiac surgery at any time were excluded. In addition, patients whose myocardial infarct involved only papillary muscle or was limited in all areas to less than 50 percent of th thickness of the left ventricular free wall or ventricular septur (subendocardium) were excluded. A total of 236 patients wer accepted for study. By *gross* inspection, transmural (in volvement of greater than the inner half of the myocardia wall) infarction of the left ventricular wall was present i each.

On the basis of reexamination of the hearts, the patient were classified into two major groups: (1) those wit transmural myocardial necrosis (acute infarct), and (2) thos with transmural myocardial fibrosis (healed infarct). Whe both fibrosis and necrosis were visible grossly in the sam heart (34 patients), the group in which the patient was place was determined by which feature was dominant by visua examination of the heart specimens. The hearts were the further subdivided by location of the left ventricular infarc into two additional groups: (1) anterior wall, and (2) posteric wall. The right ventricular free wall infarcts are shown by th diagrammatic scheme in Figure 1.

The hearts were weighed and the maximal thickness of th free wall of the right ventricle was measured. The size of bot ventricular cavities was judged normal or dilated by visua inspection. The presence or absence of ventricular thromb was recorded.

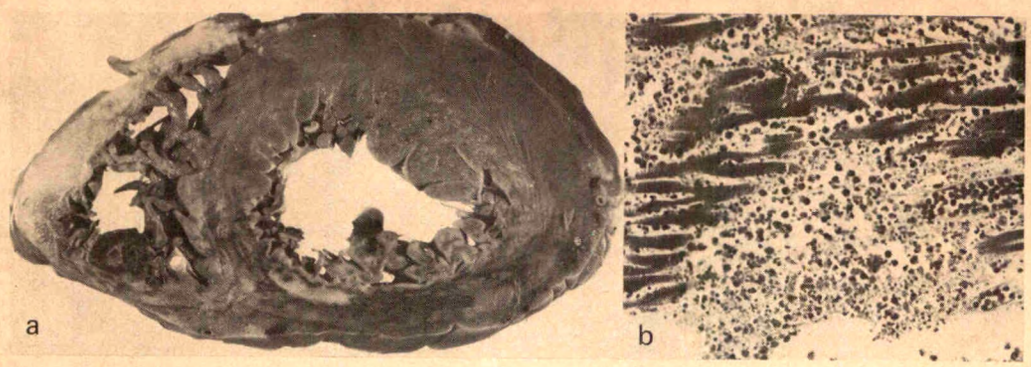


FIGURE 4. Acute right ventricular infarction. **a,** transverse slice of cardiac ventricles illustrating acute infarction of the right ventricle associated with infarction of the posterior wall of the left ventricle in an 82 year old woman who had the onset of typical clinical features of acute infarction 23 days before death. Her last 5 days were complicated by multiple arrhythmias, congestive heart failure and shock. The electrocardiogram was typical of acute myocardial infarction, posterior ("inferior") wall. **b,** photomicrograph of right ventricular wall necrosis from a 68 year old man with acute myocardial infarction involving the right ventricle (grade II), septum and posterior wall of left ventricle. Acute infarction in this patient was complicated by rupture of the ventricular septum 1 day before death. (Phosphotungstic acid hematoxylin stain ×212, reduced by 18 percent.)

The coronary arteries were excised intact and sectioned with a method described elsewhere.[1] Briefly, the excised arteries were cut at 5 mm intervals at right angles to the longitudinal axis of the vessels, and each 5 mm long segment was labeled consecutively, processed in alcohols and xylene, embedded in paraffin and cut. A single Movat-stained histologic section was examined from each 5 mm segment.

The clinical records of each of the 236 patients were reviewed. Hemodynamic data were available in 21 patients.

Results

Incidence and relation to anterior, posterior and septal infarction: Of the 236 patients, 116 had an acute and 120 had a healed left ventricular myocardial infarct. The findings in these patients are summarized in Table I and various, mainly morphologic, cardiac findings in several patients are illustrated in Figures 1 to 7. The myocardial infarcts in 236 patients involved the anterior wall in 97 patients and the posterior wall in the other 139. The age and sex of patients with anterior and posterior left ventricular myocardial infarcts were similar. Of the 97 patients with an *anterior* left ventricular infarct (acute in 60 [62 percent] and healed in 37 [38 percent]), none had an associated right ventricular infarct; of the 139 patients with a *posterior* left ventricular infarct (acute in 56 [40 percent] and healed in 83 [60 percent]), 33 (24 percent) had an associated

TABLE II

Right Ventricular Infarction: Morphologic Features

RVMI	Patients		RV Features			Grade of RV MI			
	no.	Age (yr)	D	H	T	I	II	III	IV
Acute	16	46–86 (m 65)	2	1	3	6	9	0	1
Healed	17	26–80 (m 56)	10	0	0	3	8	5	1
Totals	33	26–86 (m 62)	12	1	3	9	17	5	2

D = dilatation; H = hypertrophy; M = mean; MI = myocardial infarct; RV = right ventricular; T = thrombus.

TABLE III

Status of Right Ventricle and Coronary Arteries in Patients With Posterior Wall Left Ventricular Myocardial Infarct (MI) With and Without Associated Right Ventricular (RV) Infarct

LVMI	Cases (no.)	D (no. [%])	H (no. [%])	T (no. [%])	Patients With Histologic Study of Coronary Arteries (no. [%])			
					Total (no. [%])	With >75% Narrowing* of RCA	LAD	LCx
With RV MI	33	12[36]	1[3]	3[9]	28[85]	26[93]	20[74]	20[74]
Without RV MI	106	10[9]	5[5]	4[4]	59[56]	50[85]	46[78]	45[76]

* More than 75 percent narrowing of cross-sectional area by plaque. D = dilatation; H = hypertrophy; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

right ventricular infarct. Of the total of 236 patients, 133 had transmural infarction of the ventricular septum (Table I), 68 with anterior and 65 with posterior left ventricular infarction. All 33 patients with right ventricular infarction were among the 65 with posterior left ventricular infarction associated with transmural infarction of the ventricular septum. Of the 74 patients with posterior left ventricular infarction without associated transmural infarction of the ventricular septum, none had a right ventricular infarct. None of the patients with an isolated anterior left ventricular infarct had an associated right ventricular infarct whether or not the ventricular septum was involved.

Clinical and morphologic features: Certain clinical and morphologic features of the patients with right ventricular myocardial infarction are summarized in Tables II and III. Only 1 of the 33 patients had hypertrophy of the right ventricular wall (more than 5 mm thick), whereas 12 had right ventricular dilatation. Antemortem thrombus was found in the right ventricle of three patients. The infarct of the right ventricle wa limited to its posterior wall (types I and II) (Fig. 2 to 4 6 and 7) in 36 patients and to both the posterior an anterolateral right ventricular free walls (types III an IV) in the other 7 (Fig. 5 and 9 to 11).

Comparison of the 33 patients with a posterior lef ventricular wall infarct and associated right ventricula wall infarction and the 106 patients with a posterior lef ventricular wall infarct *without* associated right ven tricular wall infarction disclosed no significant differ ences in the patients' age, sex, length of survival afte onset of symptoms of myocardial ischemia (range 1 t 23 days [mean 8] in all groups) or the presence of righ ventricular hypertrophy or thrombus (Tables II an III). Right ventricular dilatation, however, was signifi cantly ($P < 0.05$) more frequent among the group wit a posterior left ventricular infarct and associated righ ventricular wall infarction.

Coronary arterial findings: The three major (righ left anterior descending and left circumflex) coronar

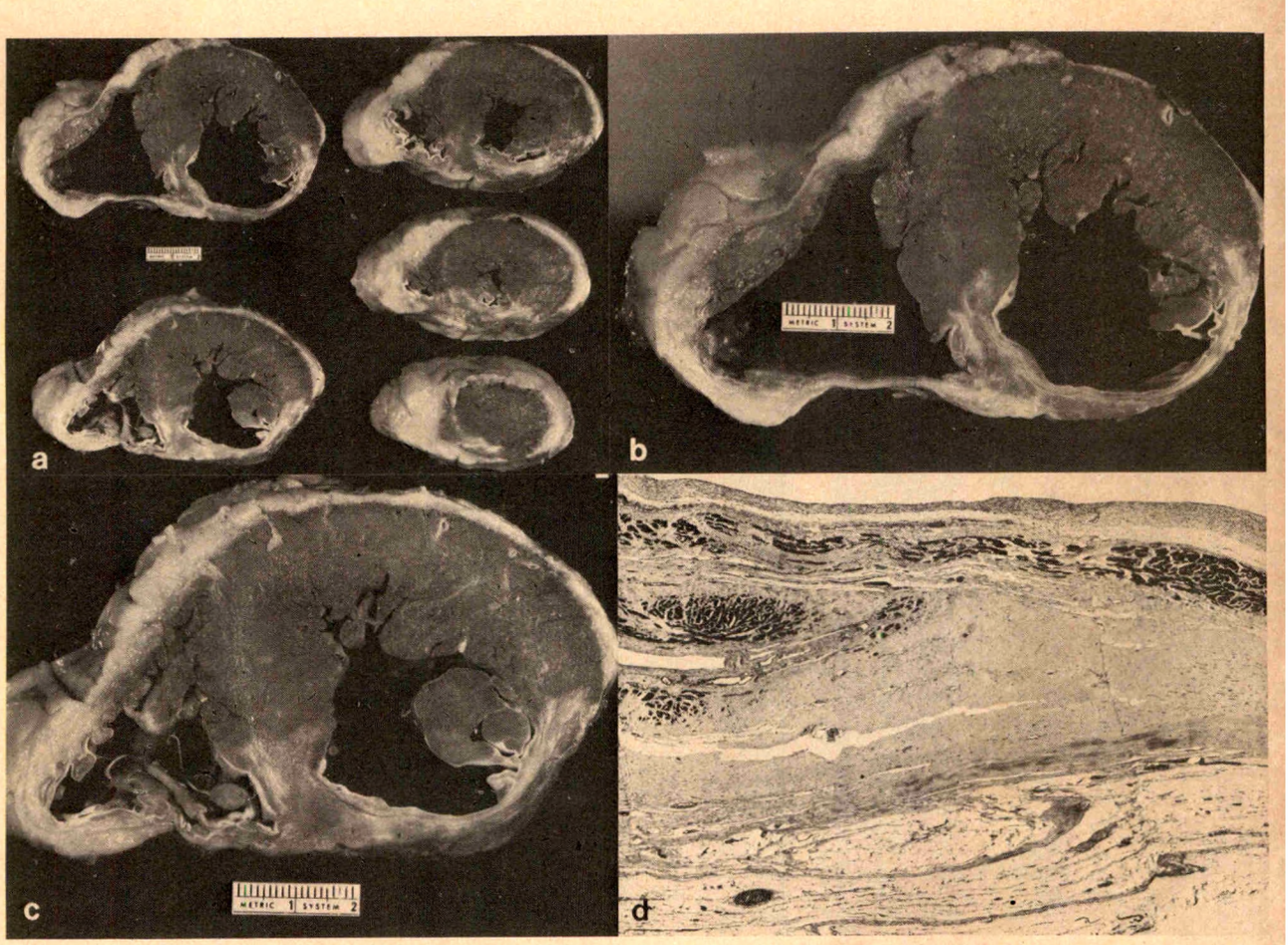


FIGURE 5. Transverse slices of cardiac ventricles **(a, b, c)** and photomicrograph of healed right ventricular infarct **(d)** from a 73 year old man wh had had an "inferior" wall myocardial infarct at age 68. The patient was subsequently treated with digoxin and diuretic agents for "mild" congestiv heart failure. He died 5 years later from complicatons of eye surgery. **a,** transverse cardiac ventricular slices. **b,** close-up view of slice at upp left in **a**. There are healed posterior right and left ventricular infarcts with thinning of the right (grade II) and left ventricular free walls and the posteri portion of ventricular septum. Both ventricular cavities are dilated. **c,** close-up view of slice at bottom left in **a,** showing additional scarring of th anterolateral wall of the right ventricle. **d,** photomicrograph showing transmural scarring of the right ventricular free wall. (Movat stain ×27, reduce by 25 percent.)

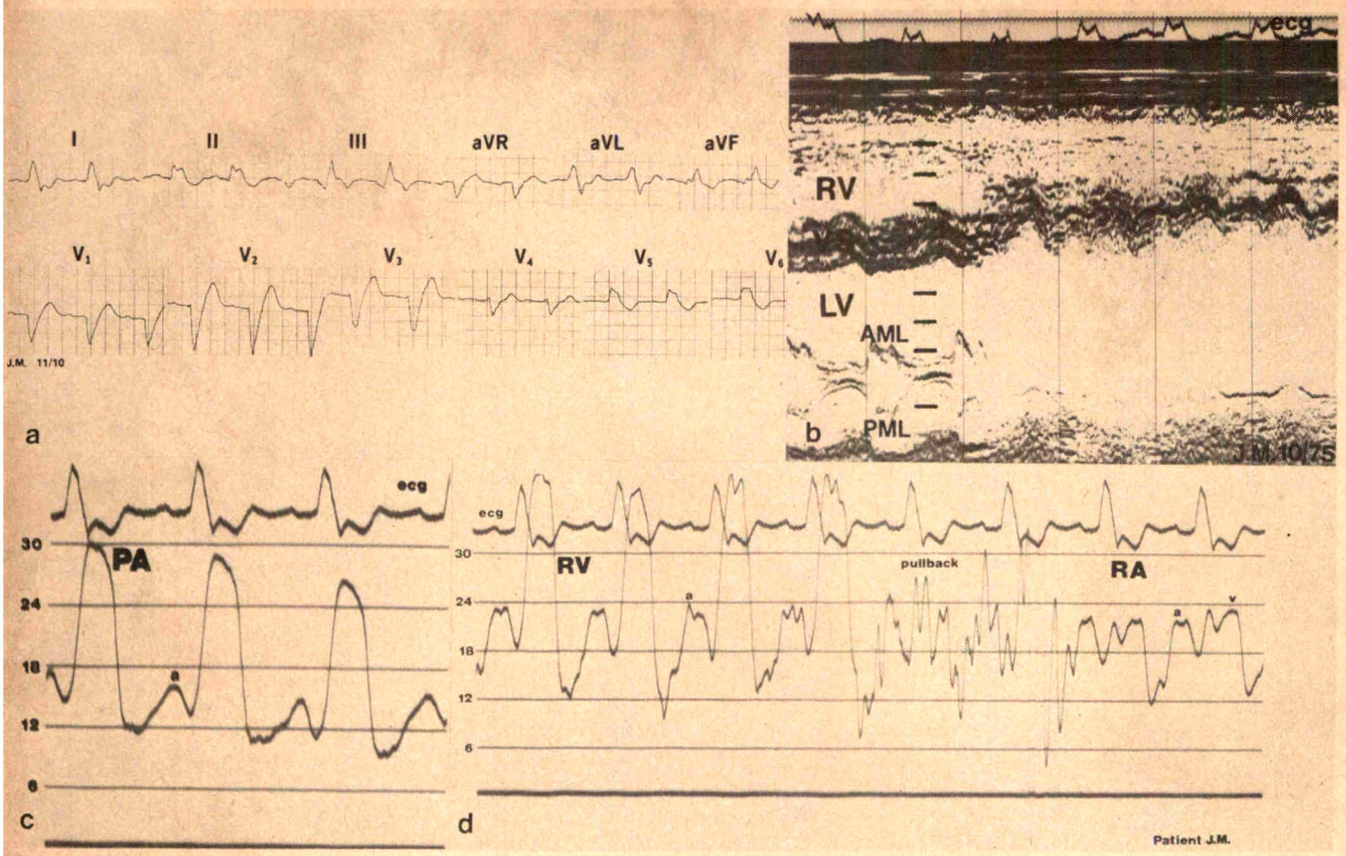


FIGURE 6. Clinical findings recorded in a 48 year old man with healed right ventricular myocardial infarction. The infarction had occurred 7 years before the recordings presented here, and the patient died of progressive congestive heart failure 2 years after the recordings. **a,** electrocardiogram showing S-T segment elevation in lead III, complete left bundle branch block and absent or small R waves in leads V_1 to V_4. **b,** echocardiogram showing biventricular dilatation and abnormal septal motion. AML = anterior mitral leaflet; LV = left ventricle; PML = posterior mitral leaflet; RV = right ventricle. **c,** pulmonary arterial (PA) pressure recording showing a prominent *a* wave. **d,** pullback tracing from the right ventricle (RV) to the right atrium (RA), demonstrating an elevated (18 mm Hg) end-diastolic pressure and prominent *a* waves in the right ventricular pressure tracing.

arteries were examined in detail in 87 (63 percent) of the 139 patients with a left ventricular posterior wall infarct (Table III). Twenty-eight of the 87 had an associated right ventricular infarct and 59 did not. No significant differences were observed among the patients with posterior left ventricular infarcts in the percent of those with and without right ventricular infarction who had more than 75 percent cross-sectional area luminal narrowing by old atherosclerotic plaques in one or more of the three major coronary arteries. The degree of narrowing of the right coronary artery was similar in the patients with and without right ventricular infarction. The percent of patients whose right coronary artery was narrowed more than 75 percent in cross-sectional area by old atherosclerotic plaque was significantly ($P < 0.05$) greater than that of patients whose left anterior descending coronary artery was narrowed to this degree, whether or not infarction involved the right ventricular wall.

TABLE IV

Right Ventricular Infarction: Hemodynamic Features

Case no.	State of MI	Grade of RV MI	Pressures (mm Hg) RA Mean	RV(s/d)	PA (s/d)	PAW Mean
1	Acute	II	5	47/10	41/25	24
2	Healed	II	5	35/5	35/15	15
3	Healed	III	7	30/5	28/12	8
4	Healed	III	23	32/23	34/20	20

MI = myocardial infarction; PA = pulmonary arterial; PAW = pulmonary arterial wedge; RA = right atrial; RV = right ventricular; s/d = systolic/diastolic.

Hemodynamic data: Of the 21 patients who had undergone cardiac catheterization, 4 had an associated right ventricular wall infarct (Table IV). In one of the four, the right atrial mean pressure was higher than the mean pulmonary arterial wedge pressure, and both the right ventricular and pulmonary arterial pressure tracings were deformed by a prominent atrial *a* wave (Fig. 6). Hemodynamic data in the other three patients with a right ventricular infarct were consistent with an isolated left ventricular wall infarct with or without left ventricular decompensation.

Comments

Although right ventricular wall infarction secondary to coronary arterial narrowing has recently received attention from the hemodynamic[2–6] and radioisotopic[7,8] standpoints, it has received little attention from a

morphologic standpoint. Of the eight previous reports mentioning infarction of the right ventricular free wall at necropsy,[2,3,7,9–13] only two[10,11] actually focused on the necropsy diagnosis of right ventricular infarction and, when an associated left ventricular infarct was present, most did not describe its location. Although four reports[7,11–13] showed photographs of infarcts of the right ventricular wall, the extent of the infarcts was rarely described or discernible in the photographs.

Right ventricular infarction: a complication of transmural posteroseptal left ventricular infarction: The present study is based on reexamination of the hearts in 236 necropsy patients with transmural left ventricular myocardial infarction secondary to coronary luminal narrowing. Of the 236 patients, 33 (14 percent) had an infarct involving the right ventricular free wall and all of them had a posteriorly located left ventricular infarct. None of the 97 patients with isolated anterior wall left ventricular infarction had associated right ventricular infarction. Thus, among patients with fatal myocardial infarction secondary to severe coronary arterial luminal narrowing, right ventricular infarction occurred only when the left ventricular infarct involved its posterior wall. Of our 139 patients with a posterior left ventricular infarct, 33 (24 percent) had an associated right ventricular infarct. Even among the patients with a posteriorly located left ventricular infarct, however, transmural infarction of the ventricular septum was a prerequisite for development of right ventricular infarction. Of the 139 patients with a posterior left ventricular infarct, 74 did not have transmural infarction of the ventricular septum and none of the 74 had an associated right ventricular infarct. In contrast, of the 65 with transmural infarction of the ventricular septum, 33 (50 percent) had an associated right ventricular infarct. Thus, *right ventricular infarction among our patients was a complication exclusively of transmural posteroseptal left ventricular infarction.*

The extent of the right ventricular necrosis or fibrosis ranged from less than one half of the posterior right ventricular free wall adjacent to the ventricular septum (nine patients) to involvement of the entire right ventricular free wall (two patients). Among the 33 patients with right ventricular infarction, the infarct was limited to the posterior right ventricular free wall in 26 (79 percent); in the remaining 7 (21 percent), both the posterior and anterolateral walls of the right ventricle were involved.

Role of right ventricular hypertrophy and dilatation: Previous investigators have proposed that right ventricular hypertrophy was either an important predisposing factor[10,14] or an absolute prerequisite[15] for the development of right ventricular myocardial infarction. The results of our study do not confirm this speculation. Right ventricular hypertrophy, in fact, was more frequent among our patients without associated right ventricular infarct. It was observed at necropsy in only 1 (3 percent) of our 33 patients *with* a right ventricular infarct, and in 12 (6 percent) of 203 patients with a left ventricular myocardial infarct unassociated with a right ventricular infarct. Furthermore, although one patient had a history of clinically diagnosed "chronic obstructive pulmonary disease," none had necropsy evidence of cor pulmonale. Although extensive right ventricular scarring has been described in various entities associated with right ventricular hypertrophy (including chronic pulmonary emboli[16] and hypertrophic cardiomyopathy[17] in the absence of significant coronary arterial luminal narrowing), such cases were excluded from the present study unless they were associated with left ventricular scarring *and* significant coronary arterial luminal narrowing.

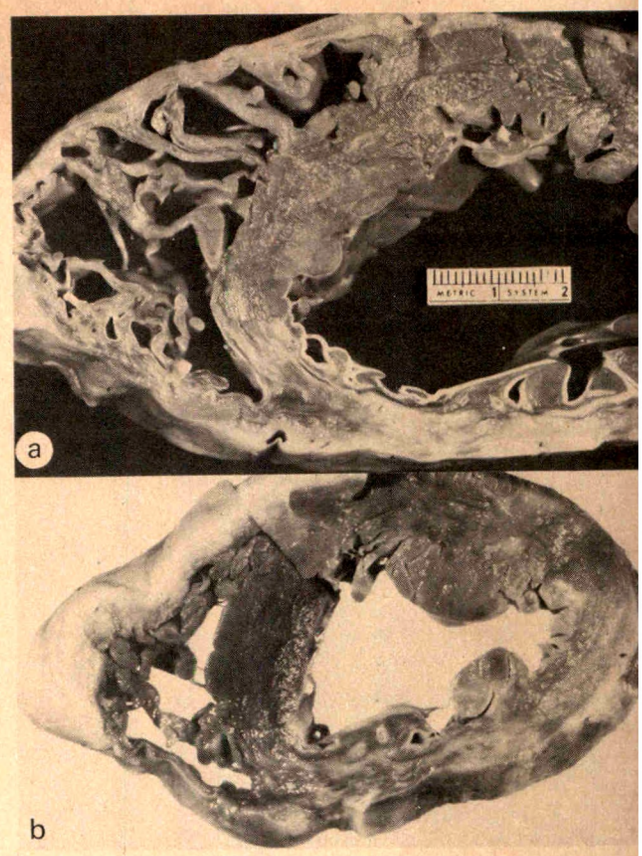


FIGURE 7. Transverse slices of cardiac ventricles showing healed right ventricular infarcts in two patients. **a,** the clinical findings in the patient whose grade III right ventricular wall infarct is shown here are shown in Figure 6. **b,** the posterior right ventricular wall is thinned and is the posterior portion of ventricular septum and posterior portion of left ventricular wall in this 56 year old woman who had an acute myocardial infarct 5 months before death.

Right ventricular dilatation was the single anatomic feature distinguishing our patients from those without right ventricular myocardial infarction. Among the 139 patients with a posterior wall left ventricular infarct, the right ventricular cavity was dilated in 12 (36 percent) of the 33 patients with and in 10 (9 percent) of 106 patients without an associated right ventricular infarct (Table III). This difference (36 versus 9 percent) is significant ($P < 0.05$). Also, for comparison, right ventricular dilatation occurred in only 16 (16 percent) of the 97 patients with an anterior wall left ventricular infarct, a significantly ($P < 0.05$) lower percent than in our patients with a right ventricular infarct.

Right ventricular mural thrombus: This is another necropsy finding reported to be more frequent among

patients with associated right ventricular wall infarction than among patients with an isolated left ventricular wall infarct.[10] However, in our 237 patients with a left ventricular wall infarct, right ventricular thrombus occurred with similar frequency in those with and in those without an associated infarct of the right ventricular wall. Of our 139 patients with a posterior wall left ventricular infarct, right ventricular thrombus occurred in 3 (9 percent) of the 33 patients with and in 4 (4 percent) of the 106 patients without an associated right ventricular infarct; of our 97 patients with an anterior wall left ventricular infarct, right ventricular thrombus occurred in 8 patients (8 percent).

Role of severe right versus left coronary arterial narrowing: Several previous investigators have noted a particularly high frequency of severe luminal narrowing by atherosclerotic plaques of the right coronary artery in patients with a right ventricular infarct associated with a left ventricular infarct. These previous studies, however, did not compare the frequency of severe narrowing of this artery among patients with a right ventricular infarct and those with an isolated left ventricular infarct. Furthermore, the previous studies did not compare the frequency of severe narrowing of the right coronary artery by atherosclerotic plaques with the frequency of severe narrowing of either the left anterior descending or left circumflex coronary artery. Among our patients with posterior wall left ventricular infarction, the percent with greater than 75 percent cross-sectional area luminal narrowing by atherosclerotic plaques of the right coronary artery was similar (about 90 percent) in the patients with and without right ventricular infarction. All our patients with right ventricular infarction had severe (greater than 75 percent cross-sectional area) luminal narrowing of the coronary artery responsible (dominant) for perfusing the posterior ventricular wall (that is, either the right or the left circumflex artery).

Clinical diagnosis: Diagnosis during life of right ventricular infarction in patients with left ventricular infarction secondary to severe coronary arterial luminal narrowing is at best difficult. If the left ventricular infarct is limited to the anterior wall, the chance of an associated right ventricular infarct is minimal. Thus, a *posterior location* of the left ventricular infarction is a prerequisite for right ventricular infarction. Nearly a quarter of all our patients with posterior wall infarction of the left ventricle had associated right ventricular infarction. Thus, if the left ventricular infarct is posterior and transmural, there is a 1 in 4 chance that there will be an associated right ventricular infarct. If, however, the ventricular septum is transmurally infarcted in association with a posterior left ventricular free wall infarction, the chance of an associated right ventricular infarction becomes 1 in 2. But the electrocardiogram is not helpful in distinguishing infarction limited to the posterior left ventricular wall from that involving both posterior and septal walls. The echocardiogram might show diminished motion of the ventricular septum in this circumstance, but the reliability of this technique to determine transmural septal infarction is unproved. One finding suggestive of right ventricular infarction is right ventricular dilatation, an occurrence nearly 3 times more frequent in our patients with than in those without right ventricular infarction. Right ventricular hypertrophy is rare in patients with right ventricular infarction secondary to coronary narrowing and is therefore not helpful from a diagnostic standpoint.

Hemodynamic findings: role in clinical diagnosis: Before the introduction of newer, noninvasive techniques, the clinical diagnosis of right ventricular myocardial infarction had been limited to cardiac catheterization. The finding of elevated right atrial (or right ventricular end-diastolic) pressure out of proportion to left atrial (or left ventricular end-diastolic) pressure has been suggested as the characteristic hemodynamic profile of right ventricular infarction.[2] Such hemodynamic abnormalities have been confirmed in at least five patients by necropsy.[2,3,7,13] No previous reports, however, have described hemodynamic findings in patients in whom the diagnosis of right ventricular myocardial infarct was first established at necropsy. Three of our four patients with necropsy-confirmed right ventricular myocardial infarction had a hemodynamic profile that was *not* suggestive of associated right ventricular infarction (Table IV). The nondiagnostic hemodynamics in at least one of these three patients were not simply a function of the temporal relation of the catheterization to the infarction because the right-sided cardiac catheterization was performed during the period of acute myocardial infarction. An alternative explanation for the nondiagnostic hemodynamic findings in one or all three of these patients is that they were obscured by relative hypovolemia. Rigo et al.[7] described two patients with cardiogenic shock and a low left ventricular filling pressure in whom the characteristic hemodynamic profile of right ventricular infarction complicating left ventricular infarction was unmasked by volume administration. Thus, it is possible that had our three patients with right ventricular infarction and "nondiagnostic" hemodynamics been stressed with volume or exercise, diagnostic hemodynamic findings might have developed.

Nevertheless, it appears that the hemodynamic profile previously considered characteristic of right ventricular infarction is less diagnostically sensitive than thought and that right ventricular infarction may occur in the presence of normal or near normal intracardiac pressures. Conversely, in the absence of pericardial or valvular heart disease, the hemodynamics described for right ventricular infarction appear to be relatively specific. Hemodynamic findings in 17 other necropsy patients with left ventricular infarction without associated right ventricular infarction disclosed no intracardiac pressure recordings typical of those observed in patients with right ventricular infarction, that is, no false positives.

Simulation of hemodynamics of constrictive pericarditis: The intracardiac pressures characteristic of right ventricular infarction may persist for years after anatomic healing of the infarct, and these pressure tracings may simulate those observed in patients with pericardial heart disease. Our Patient 4 (Table IV) at cardiac catheterization performed 2 years after healing

of the acute myocardial infarct still had hemodynamics characteristic of those observed during the period of acute infarction (Fig. 6). Furthermore, the pressure tracings in this patient disclosed prominent *a* waves in both the right ventricle and major pulmonary arteries, findings identical to those described in patients with constrictive pericarditis. Raabe and Chester[13] and Lorell et al.[3] recently pointed out that among patients with acute left ventricular infarction associated with right ventricular infarction the intracardiac hemodynamics could simulate those in patients with pericardial constriction. As in patients with combined acute right and left ventricular wall myocardial infarcts, the characteristic hemodynamic abnormalities in patients with pericardial constriction may not be manifest until the patients are stressed with volume loading or with exercise.[18]

Clinical recognition and determinants of right ventricular dysfunction: Cumulative clinical experience with right ventricular myocardial infarction complicating left ventricular myocardial infarction has clearly established the existence of a specific hemodynamic syndrome of right ventricular dysfunction characterized by underfilling of the left ventricle as a result of impaired right ventricle contractility.[2–8,13] In such patients, right ventricular dilatation is the sole compensatory mechanism by which right ventricular contractility may be augmented. Under such circumstances, volume administration may be critical to maintain a maximal right ventricular filling pressure. Indeed, supplemental volume administration in patients with *elevated* right-sided pressures and a *normal* or near-normal left ventricular filling pressure (that is, patients with right ventricular infarction) has produced marked hemodynamic improvement. Thus, it becomes important to recognize clues to the often occult syndrome of right ventricular dysfunction or right ventricular infarction. Our study suggests that evidence of an "inferior" myocardial infarct combined with evidence of right ventricular dilatation should make one particularly suspicious of the presence of right ventricular infarction.

The amount of hemodynamic data available in patients with proved right ventricular infarction is inadequate to permit conclusions regarding the relation between the extent of the right ventricular infarct and the degree of hemodynamic decompensation. It is likely that the ability of the right ventricle to contribute adequately to left ventricular filling is more a function of the integrity of the ventricular septum than of the integrity of the right ventricular free wall. Starr et al.[19] and others[20,21] have demonstrated in dogs that experimental destruction of the right ventricular free wall does not produce adverse hemodynamic consequences. The contribution of the contracting ventricular septum is apparently great enough to compensate for the loss of participation of the right ventricular free wall. It might be expected that an infarct limited to the juxtaseptal portion of the right ventricular free wall (grade I) or even limited to the entire posterior wall (grade II) would be too small to affect right ventricular function. Yet of our 12 patients with right ventricular dilatation in association with right ventricular infarction, 11 had right ventricular infarction limited to the posterior wal (grade I in 3 and grade II in 8). If right ventricular dilatation constitutes a sign of right ventricular dysfunction, then the latter was not simply a function of the anatomic extent of the right ventricular infarct. It is more likely that the extent of septal involvement (present to a greater degree in all our patients with a right ventricular infarct) was the principal determinant of right ventricular decompensation. In addition, acute myocardial ischemia can in itself lead to acute reduction in ventricular contractility.

Newer, noninvasive methods of diagnosis: Recent reports of echocardiographic and radioisotopic findings in patients with acute myocardial infarction suggest that it may be possible to establish the diagnosis of right ventricular myocardial infarction reliably by noninvasive means. Sharpe et al.[8] demonstrated right ventricular dilatation with M mode echocardiography in five of six patients with acute right ventricular myocardial infarction. Similar results were demonstrated with gated scintigraphy.[7] The frequency of right ventricular dilatation among our patients with right ventricular infarction supports the validity of these noninvasive findings in patients with right ventricular infarction. Additional abnormalities demonstrated on radioisotopic studies in patients with right ventricular infarction include segmental or generalized right ventricular contraction abnormalities and increased right ventricular uptake of technetium pyrophosphate. Of the five patients described by Sharpe et al.[8] with increased uptake of this radionuclide in the right ventricular free wall each had increased uptake in the ventricular septum and posterior left ventricle. This observation is consistent with our finding of consistent involvement of the septum and posterior wall of the left ventricle in patients with right ventricular myocardial infarction.

Role of coronary blood supply to right ventricle: The basis for the apparently exclusive association of right ventricular infarct with infarction of the posterior wall of the left ventricle may be the specific anatomy of the coronary blood supply to the right ventricle. The bulk of the right ventricular myocardium is consistently supplied by numerous branches of the coronary artery supplying the posterior wall of the left ventricle (usually [90 percent[22]] the right coronary artery); with a left dominant system, the circumflex coronary artery supplies both right ventricular and posterior left ventricular branches. Thus, infarction of the right ventricle can result only when the vascular supply to the posterior wall of the left ventricle is compromised as well. In contrast, the anteriormost portion of the right ventricle including the anterior paraseptal region, has a *dual* blood supply that consists of right ventricular branches from the left anterior descending coronary artery and most importantly, the conus branch of the right coronary artery. The latter is insurance for the right ventricle in cases of anterior left ventricular infarction; conversely, atherosclerotic narrowing of the right coronary artery proximal to or involving the conus branch probably accounts for most cases of circumferential (type IV) right ventricular myocardial infarction.

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Correlation Between Myocardial Structure and Diastolic Properties of the Heart in Chronic Aortic Valve Disease: Effects of Corrective Surgery

FRANZ SCHWARZ, MD
WILLEM FLAMENG, MD
JUTTA SCHAPER, MD
FRITZ HEHRLEIN, MD

Bad Nauheim and Giessen, West Germany

Left ventricular end-diastolic properties were evaluated with cineangiography and pressure measurements before and 6 months after aortic valve replacement with a Björk-Shiley prosthesis in 10 patients with aortic stenosis, 7 patients with mixed aortic valve disease and 7 patients with aortic insufficiency. Mean left atrial pressure, left ventricular end-diastolic pressure, volume and wall thickness were measured, and the stiffness constant K_A and the elastic stiffness E_m were calculated. Myocardial cell diameter and the degree of myocardial fibrosis were determined with morphometric analysis of transmural needle biopsy specimens obtained from the left ventricular free wall at operation. Significant correlations were found between myocardial cell diameter and end-diastolic pressure ($r = 0.63$), mean left atrial pressure ($r = 0.58$), end-diastolic wall thickness ($r = 0.80$), K_A ($r = 0.56$) and E_m ($r = 0.53$). However, no significant correlation existed between percent fibrosis and any of these measurements. Before operation, end-diastolic left ventricular pressure, mean left atrial pressure, K_A and E_m were significantly elevated in aortic stenosis and mixed aortic valve disease but not in aortic insufficiency. After valve replacement clinical improvement was seen in all patients. End-diastolic left ventricular pressure, mean left atrial pressure, end-diastolic volume and E_m decreased and normalized completely in all groups. End-diastolic wall thickness and K_A decreased significantly in aortic stenosis and mixed aortic valve disease (not in aortic insufficiency) but remained moderately elevated. Close correlations were found between end-diastolic wall thickness and K_A ($r = 0.78$) and between mean left atrial pressure and E_m ($r = 0.85$).

These results suggest (1) myocardial cell diameter, but not myocardial fibrosis, is a major determinant of end-diastolic properties of the left ventricle in chronic aortic valve disease. (2) Corrective surgery with a Björk-Shiley valve causes normalization of elastic stiffness of the chamber and of mean left atrial pressure, thus explaining the alleviation of congestive symptoms.

The effect of myocardial fibrosis and hypertrophy on the diastolic properties of the left ventricle in a chronically overloaded heart is still disputed. There is a general agreement that the manifestations of congestive heart failure in a hypertrophied heart are closely related to abnormalities of chamber stiffness.[1–3] These abnormalities may or may not be associated with alterations in muscle stiffness. Recent clinical studies indicated that increased chamber stiffness occurs in chronic pressure overload, a finding that may help to explain the pathophysiologic features of pulmonary congestion in patients with such overload. In contrast, there is no general agreement about myocardial chamber stiffness in patients with chronic volume overload, although it was suggested[3] that intrinsic muscle stiffness may be increased because of increased fibrotic content of the myocardium.

From the Kerckhoff-Institut, Max-Planck-Gesellschaft, Bad Nauheim and from the Department of Cardiovascular Surgery, Justus-Liebig University, Giessen, West Germany. Manuscript received April 18, 1978; revised manuscript received July 11, 1978, accepted July 12, 1978.

Address for reprints: Franz Schwarz, MD, Zentrum für Innere Medizin, Abt. III, Justus-Liebig Universität, Rodthohl 6, D-6300 Giessen, West Germany.

The influence of corrective surgery on the diastolic properties of the left ventricle was only rarely evaluated in clinical studies. Gault et al.[4] described conflicting results in a small series of patients with chronic volume overload. Experimental data,[5,6] on the other hand, indicated that hypertrophy and stiffness changes may be reversible in chronic volume overload. To our knowledge no previous study has attempted to quantitate the structural alterations of the myocardium and to compare the myocardial structure with the diastolic hemodynamic properties of the left ventricle. We therefore quantitated the degree of myocardial fibrosis and hypertrophy with morphometric analysis of biopsy material from patients who underwent aortic valve replacement for chronic pressure or volume overload. Postoperative hemodynamic studies were carried out to evaluate the effect of aortic valve replacement on the diastolic properties of the left ventricle.

Methods

Patients

Initially, 28 consecutive patients with isolated aortic valve disease were studied 2 to 6 weeks before aortic valve replacement. The data of four patients with paravalve aortic regurgitation after surgery are not included. Sixteen of the remaining 24 patients could be restudied 6.6 ± 2.2 (mean ± standard deviation) (range 5 to 12 months) after aortic valve replacement with a Björk-Shiley tilting disc valve prosthesis. Patients 14, 16 and 22 (Table I) died in the early postoperative phase; five other patients refused the second investigation.

Before surgery, predominant aortic stenosis was found in 10 patients, mixed aortic valve disease in 7 and predominant aortic insufficiency in 7 (Table I). Associated mitral valve disease was excluded in all patients after analysis of simultaneously recorded left atrial and left ventricular pressure curves and, when necessary, after obtaining an additional left ventricular angiogram. Obstructive coronary artery disease was not found in any patient during selective coronary arteriography. Functional class (New York Heart Association criteria[7]) was estimated before and after surgery by evaluating symptoms commonly associated with aortic valve disease: angina, syncope or presyncope and dyspnea. The electrocardiogram before and after surgery was analyzed according to the criteria of Romhilt and Estes[8] for left ventricular hypertrophy, and cardiothoracic ratio was measured preoperatively and at the time of restudy.

All patients underwent open heart surgery for aortic valve replacement. Through cannulation of the iliac artery, total cardiopulmonary bypass with a roller pump and a disposable bubble oxygenator was used. Decompression of the left ventricle was accomplished by a left ventricular vent. Preservation of the myocardium was attained by the use of cardioplegic arrest of the heart. Age, sex, functional class, electrocardiogram, cardiothoracic ratio, peak left ventricular to aortic pressure gradient and degree of aortic regurgitation[9] are listed in Table I.

Procedures

Patients with aortic valve disease were studied before and after surgery without premedication in the same catheterization laboratory and with the same equipment. All patients were receiving digoxin before and after surgery. A no. 8.5F Brockenbrough catheter was positioned in the left ventricle transseptally after puncture of a femoral vein and a no. 8F pigtail catheter in the ascending aorta retrograde by way of the femoral artery. Before injection of contrast material, phasic and mean atrial pressure, left ventricular end-diastolic pressure and peak systolic pressure were measured using Statham P23Db pressure transducers and recorded on an Oscillomink direct-writing system. The end-diastolic pressure was measured during midinspiration at the peak of the R wave of the simultaneously recorded lead II electrocardiogram. The catheter manometer systems tested in vitro on a sine wave pressure generator had a uniform amplitude response up to 30 hertz. Single plane 35 mm cineangiograms of the left ventricle were filmed in midinspiration at 48 frames/sec in the 30°

TABLE I

Clinical Data in 24 Patients Before (B) and After (A) Operation for Aortic Valve Disease (mean ± SD)

	Age (yr)	Sex	NYHA Class B	NYHA Class A	Romhilt-Estes Score B	Romhilt-Estes Score A	Cardiothoracic Ratio B	Cardiothoracic Ratio A	PPSG (mm Hg) B	PPSG (mm Hg) A	AR B	AR A
Control group (7 subjects)	43.3 ± 8.4	5M, 2F	...	...	0.4 ± 0.5	...	0.43 ± 0.03	...	...	...	...	...
Aortic stenosis (10 patients)	45.5 ± 7.3	8M, 2F	2.8 ± 0.4	1.1 ± 0.4	4.8‡ ± 1.9	0.9 ± 1.2	0.53† ± 0.06	0.45 ± 0.05	85.9 ± 40.4	16.0 ± 7.1	1.5 ± 0.7	0
P value (B vs A)			<0.001		<0.001		<0.01		<0.05		<0.05	
Aortic stenosis + insufficiency (7 patients)	37.1 ± 7.2	7M	3.4 ± 0.5	1.3 ± 0.5	8.9‡ ± 1.1	1.0 ± 0.9	0.59† ± 0.10	0.47 ± 0.07	64.6 ± 25.8	10.8 ± 14.8	3.9 ± 0.7	0.2 ± 0.5
P value (B vs A)			<0.001		<0.001		<0.05		<0.001		<0.001	
Aortic insufficiency (7 patients)	34.7 ± 17.1	5M, 2F	3.0 ± 0.0	1.3 ± 0.5	3.6* ± 1.9	1.0 ± 1.4	0.51† ± 0.06	0.49 ± 0.07	1.7 ± 4.5	10.7 ± 12.1	3.9 ± 0.7	0.2 ± 0.4
P value (B vs A)			<0.001		<0.01		NS		NS		<0.001	

* Probability (P) <0.05; † P <0.01; ‡ P <0.001 compared with control values.
AR = aortic regurgitation estimated from aortic root angiogram; NS = not significant (P >0.05); NYHA class = New York Heart Association functional classification; PPSG = peak to peak left ventricular to aortic pressure gradient.

right anterior oblique projection after injection of 50 ml of Urografin-76® into the left ventricle through the Brockenbrough catheter. Simultaneously the aortic pressure and the electrocardiogram were recorded with a paper speed of 100 mm/sec. No mitral regurgitation was detected during normally conducted sinus beats during this procedure. In all patients aortic root angiography was performed to estimate the degree of aortic regurgitation.[9] Thereafter coronary angiography was carried out using the Judkins technique.

Seven patients without heart disease were studied according to the same protocol to provide control hemodynamic data. These patients were studied because of chest pain but they were found to have normal hemodynamics and a normal coronary arteriogram and left ventriculogram.

Measurements of left ventricular hemodynamic properties: From the cineangiograms silhouettes were drawn of the left ventricular cavity at end-diastole and end-systole. The first well opacified beat was chosen for analysis; extrasystolic and postextrasystolic beats were not analyzed. Th long axis (L) of the left ventricle was taken as the longes measured line from the apex to the aortic valve. The mino axis (M) was calculated as $M = 4 \cdot A/\pi \cdot L$, where A = area de termined by planimetry. Ventricular volumes were calculate using the single plane area-length method[10] (volume = $\pi/6 \cdot M^2L$). Correction factors for magnification and pincushio effect were obtained from a grid filmed in the plane occupie by the left ventricle. The regression equation of Kasser an Kennedy[10] was used. In 15 patients without heart disease w found no significant difference between stroke volume as sessed angiographically and that assessed from manuall checked cardiac output determinations obtained with th thermodilution technique[11] (no. 7F Swan-Ganz thermodilu tion catheter coupled to a cardiac output computer, Fa. Die fenbach Ffm., and to a Kipp B12 direct-writing system) Stroke volume assessed with thermodilution was 45.4 ± 10. ml/m^2 (mean ± standard deviation) compared with the an

TABLE II

Hemodynamic Data in 24 Patients Before (B) and After (A) Operation

Case no.	Cell Diameter (μ)	% Fibrosis	EDP (mm Hg) B	EDP (mm Hg) A	MLAP (mm Hg) B	MLAP (mm Hg) A	EDVI (ml/m^2) B	EDVI (ml/m^2) A	h_D (cm) B	h_D (cm) A	K_A B	K_A A	E_m (10^3 dynes/cm^2) B	E_m (10^3 dynes/cm^2) A
Control Group (7 subjects)														
Mean ± SD	...		9.4 ± 2.2	...	7.6 ± 2.5	...	92.4 ± 18.2	...	0.94 ± 0.12	...	16.7 ± 1.3	...	391 ± 122	...
Aortic Stenosis (10 patients)														
8	...	22	22	10	10	5	91.5	51.2	1.86	1.78	25.0	22.8	618	201
9	45	10	33	14	25	7	130.2	74.6	1.68	1.36	25.2	21.2	1187	422
10	33	14	32	11	12	6	130.8	108.6	1.43	1.23	23.7	17.9	1315	374
11	...	8	28	20	14	6	72.4	64.7	1.32	0.92	24.3	20.4	987	867
12	39	17	19	...	11	...	106.9	...	1.56	...	23.5	...	672	...
13	33	14	25	...	22	...	97.0	...	1.55	...	23.9	...	786	...
14	27	13	18	...	23	...	73.3	...	1.29	...	22.7	...	552	...
15	39	19	32	...	24	...	138.9	...	1.60	...	24.7	...	1183	...
16	30	19	23	...	14	...	111.4	...	1.36	...	21.9	...	926	...
17	...	...	9	13	8	7	74.9	63.2	1.64	1.09	21.2	20.2	195	412
Mean ± SD	35.1 ± 6.2	15.1 ± 4.5	24.1‡ ± 7.6	13.6* ± 3.9	16.3† ± 6.5	6.2 ± 0.8	102.7 ± 25.1	72.5 ± 21.8	1.53‡ ± 0.18	1.28 ± 0.33	23.6‡ ± 1.3	20.5† ± 1.8	842† ± 345	455 ± 24
$P^§$			NS		NS		<0.05		<0.05		<0.05		NS	
Aortic Stenosis + Insufficiency (7 patients)														
18	...	20	28	...	22	...	144.0	...	1.19	...	21.6	...	1354	...
19	54	16	41	9	38	5	211.1	61.1	1.79	1.52	24.6	19.9	1786	217
20	42	17	22	12	19	15	161.2	98.4	1.42	1.43	21.7	18.9	879	344
21	30	17	32	9	32	7	203.2	68.2	1.42	1.28	22.7	18.7	1473	258
22	...	23	38	...	36	...	264.8	...	1.37	...	22.5	...	2056	...
23	42	18	28	20	22	15	228.5	135.8	1.45	1.22	22.1	20.5	1286	867
24	...	...	32	14	17	13	131.7	77.2	1.34	0.96	23.0	18.6	1417	591
Mean ± SD	42.0 ± 9.8	18.5 ± 2.6	31.6‡ ± 6.4	12.8 ± 4.6	26.6‡ ± 8.6	11.0 ± 4.7	192.1‡ ± 48.3	88.1 ± 30.1	1.43‡ ± 0.18	1.28‡ ± 0.22	22.6‡ ± 1.0	19.3† ± 0.8	1464‡ ± 374	455 ± 27
$P^§$			<0.05		NS		<0.01		<0.05		<0.01		<0.05	
Aortic Insufficiency (7 patients)														
25	...	20	20	6	...	5	229.1	72.9	1.30	1.41	19.9	17.5	945	140
26	...	22	11	14	14	10	147.0	132.3	1.47	1.43	18.5	19.7	381	508
27	24	18	15	10	9	4	168.0	91.3	1.24	1.30	18.7	18.4	671	322
28	36	15	15	11	10	8	140.0	90.0	1.24	1.21	18.7*	19.0	567	355
29	21	8	15	8	9	5	169.4	71.8	0.79	1.05	17.2	17.3	908	253
30	33	20	9	14	8	5	170.0	126.8	1.18	1.03	16.6	18.3	354	628
31	30	14	6	...	4	...	153.6	...	1.03	...	14.7	...	223	...
Mean ± SD	28.8 ± 6.2	16.7 ± 4.8	13.0 ± 4.7	10.5 ± 3.2	9.0 ± 3.2	6.2 ± 2.3	168.2‡ ± 29.4	97.5 ± 26.2	1.18* ± 0.22	1.24† 0.17	17.8 1.7	18.4* 0.9	536 233	368 176
$P^§$			NS		<0.05		<0.05		NS		NS		NS	

§ Probability value (B versus A): * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

EDP = left ventricular end-diastolic pressure; EDVI = left ventricular end-diastolic volume; E_m = elastic stiffness; h_D = end-diastolic wall thickness of left ventricle; K_A = stiffness constant; MLAP = mean left atrial pressure; NS = $P > 0.05$; SD = standard deviation.

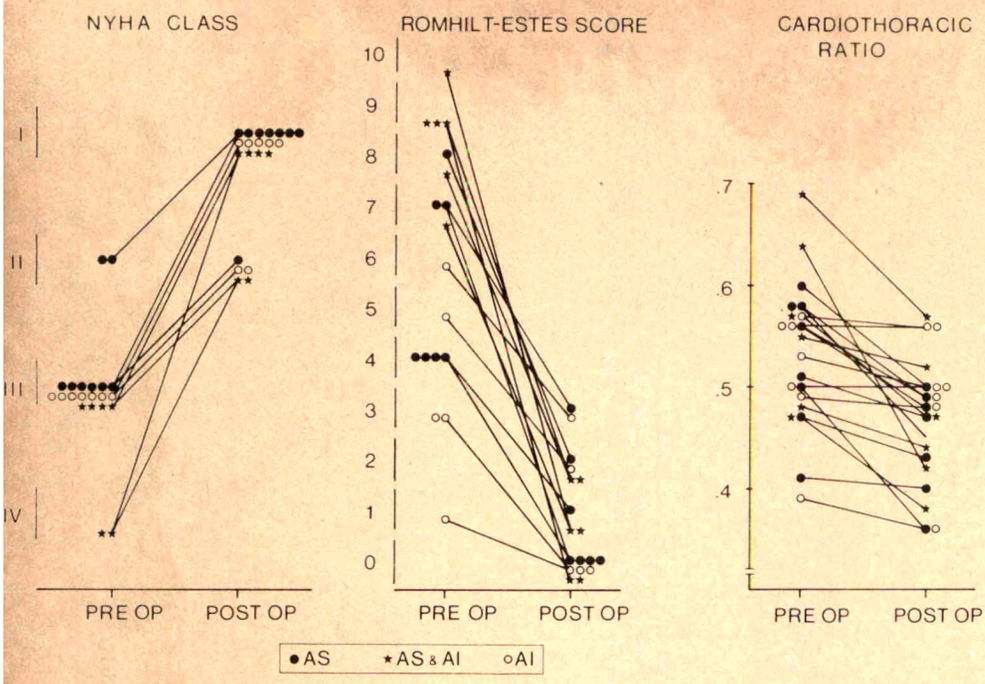


FIGURE 1. Individual preoperative and postoperative data for New York Heart Association (NYHA) functional classification, Romhilt-Estes score for left ventricular hypertrophy and cardiothoracic ratio in patients with aortic valve disease. Significant changes occurred in the different groups after aortic valve replacement. AI = aortic insufficiency before operation; AS = aortic stenosis before operation; AS & AI = aortic stenosis and aortic insufficiency; PRE OP = preoperative value; POST OP = postoperative value.

giographic value of 44.8 ± 10.2 ml/m^2. These values are in close agreement with the data reported by others[12] in normal persons.

A representative measurement of left ventricular wall thickness was made from the right anterior oblique projection of the ventriculogram in end-diastole at a point approximately between the apex and the aortic valve.[13] Left ventricular wall volume was calculated according to the method of Rackley et al.[14] as modified by Trenouth et al.[15] with the formula

$$V_W = (V_{C+W} - V'),\ V_{C+W} = \frac{4}{3}\pi\left(\frac{M}{2} + h\right)^2\left(\frac{L}{2} + \frac{h}{2}\right)$$

where V_w = left ventricular wall volume; V_{C+W} = volume (V) of left ventricular cavity (C) plus wall (W); V′ = end-diastolic volume′ and h = left ventricular wall thickness at the minor equator at end-diastole.

Diastolic properties of the left ventricle were estimated from the formulas suggested by Mirsky and Parmley.[16] The stiffness constant K_A was calculated as:

$$K_A = 3(1 + \log_e 2.33\ P_{ed})(1 + 1/[v + v^{1/3} \cdot (1 + v)^{2/3}])$$

where, v = end-diastolic volume divided by left ventricular wall volume; and P_{ed} = end-diastolic pressure.

The end-diastolic wall stress at the mid wall (σ_m) was estimated assuming spheric geometry as:

$$\sigma_m = P(V/V_W)(1 + b^3/2R^3)$$

where P = pressure; V = left ventricular volume; V_W = left ventricular wall volume; b = external radius of the sphere including V_W; a = internal radius; and R = radius at the mid wall (R = [a + b]/2). The elastic stiffness of the ventricular chamber (E_m) was approximated as:

$$E_m = K_A\sigma_m.$$

Collection and Preparation of Tissue

Tissues were obtained from each patient with biopsy at the time of open heart surgery. Operation was performed with the patient on cardiopulmonary bypass, utilizing a disposable bubble-type oxygenator. We used a Tru-cut biopsy needle (Travenol Laboratories) to take transmural biopsy specimens from the left ventricular anterior free wall. The specimens were taken before cross-clamping of the aorta from the beating heart. Immediately after biopsy the tissues were fixed in cacodylate-buffered 6 percent glutaraldehyde. After immersion fixation for 24 hours at 4° C the samples were rinsed in 0.1 molar cacodylate buffer with 7.5 percent sucrose during 12 hours at 4° C. After postfixation for 1 hour in 2 percent osmium oxide in veronalacetate buffer at pH 7.4 with 4 percent sucrose at 4° C, the tissues were dehydrated in graded series of ethanol, treated with propylene oxide and embedded in Epon 812. After polymerization semithin sections of 1 to 2 μm thickness were prepared and stained with alkaline toluidine blue. Each block measured 1 to 4 mm^2 in area.

Morphometry was carried out with the light microscope using a special grid with vertical and horizontal lines providing 110 intersections (points). According to the basic principles of morphometry[17] counting of the number of points overlying a certain structure results in quantitative determination of the volume of the structure under investigation in relation to the volume of the entire tissue under the square grid. Therefore, the total number of points was regarded as 100 percent and the points counted in the fibrotic area were expressed as the percent of the entire tissue within the limits of the grid. The axis of the square grid was then rotated approximately 45°, and determination of the points was repeated. After a random sampling procedure a different part of the same section was chosen and the points overlying fibrotic areas were counted with the grid in control position and after rotation of 45°. This way, two different areas of each section were counted twice. Only longitudinal sections at a magnification of ×250 were evaluated, and blood vessels and perivascular interstitial cells were excluded from the fibrotic area. For each patient between three and nine tissue samples and from each sample two sections were counted. The myocardial cell diameter was measured in longitudinal sections by a micrometer-eyepiece which was calibrated. At least 10 measurements were obtained for each tissue sample and the results averaged to get a representative measurement for each patient (Table II).

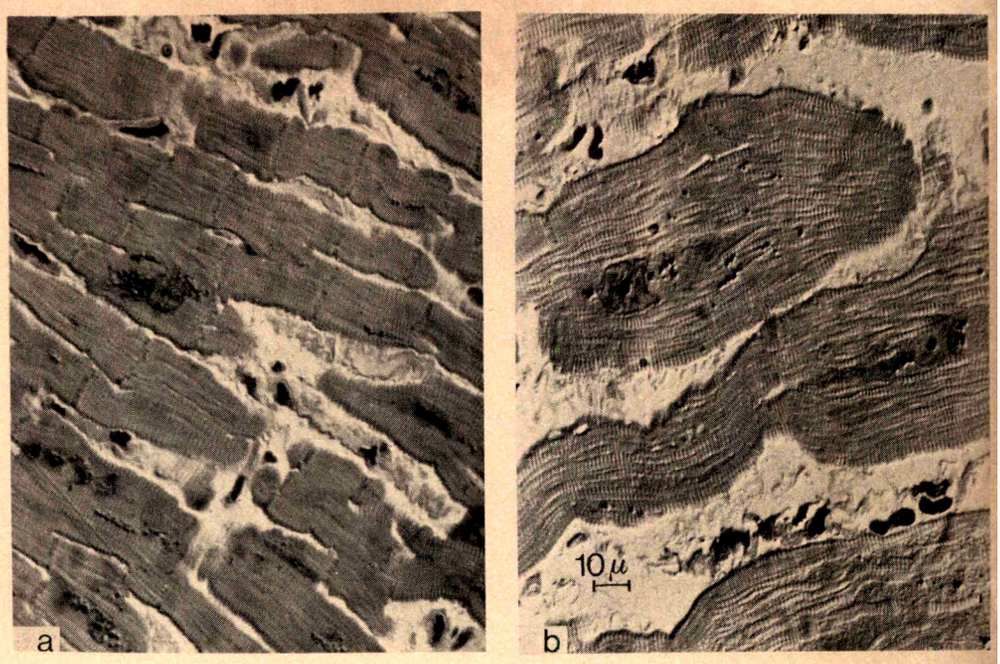


FIGURE 2. Light micrographs of myocardial tissue. **a,** in a patient with aortic insufficiency. The cells are small in diameter. **b,** in a patient with aortic stenosis plus insufficiency. Cell diameter is greater than in the patient with aortic insufficiency. (×250, reduced by 23 percent.)

Pre- and postoperative data were compared using Student's *t* test for paired data. Different groups were compared using Student's *t* test for unpaired data.

Results

Clinical data (Table I): Patients with aortic stenosis were restudied by catheterization 6.0 ± 0.8 months (mean ± standard deviation), patients with mixed valve disease 6.7 ± 2.9 months and patients with aortic insufficiency 6.7 ± 2.1 months after valve implantation. The size of Björk-Shiley prosthesis used was 25.6 ± 1.4, 26.4 ± 1.9 and 27.0 ± 1.8, respectively, in these three groups of patients with aortic valve disease.

All patients showed improvement in functional class, Romhilt-Estes score for left ventricular hypertrophy and cardiothoracic ratio after valve replacement as shown by the individual data in Figure 1 and the group values in Table I. In patients with aortic insufficiency the cardiothoracic ratio decreased, but the reduction was not statistically significant ($P > 0.05$). The Romhilt-Estes score and the cardiothoracic ratio in all three groups did not differ from values in the normal control group. The transvalve gradient decreased significantly in patients with aortic stenosis and in those with mixed aortic valve disease. A residual transprosthetic pressure gradient was found in all three groups after operation and ranged between 0 and 36 mm Hg.

Relation between myocardial structure and diastolic properties of the hypertrophied left ventricle (Tables II and III): A wide range of myocardial cell diameters was found. Typical examples of different degrees of hypertrophied cells are shown in Figure 2. The average cell diameter was greater in mixed aortic valve disease than in aortic insufficiency ($P < 0.05$). Linear regression analysis was carried out to determine the effect of cell diameter on diastolic function of the left ventricle. Myocardial cell diameter was significantly related to the following variables (Table III): end-diastolic left ventricular pressure ($r = 0.63$, $P < 0.01$), mean left atrial pressure ($r = 0.58$, $P < 0.05$), end-diastolic left ventricular wall thickness ($r = 0.80$, $P < 0.001$), stiffness constant K_A ($r = 0.56$, $P < 0.05$) and elastic stiffness E_m ($r = 0.53$, $P < 0.05$). Figure 3 illustrates the relation between cell diameter and end-diastolic wall thickness. It is evident that the relation is mainly influenced by the type of overload: Pressure overload produces more augmentation of cell diameter and wall thickness than volume overload. However, within the group with aortic stenosis, a significant relation between diameter and wall thickness was also found ($r = 0.94$, $P < 0.01$), thus illustrating that the degree of pressure overload is the main factor that induces an increase in cell diameter.

Interstitial myocardial fibrosis ranged between 8 and 23 percent. No significant relation was found between percent fibrosis and the following values (Table III): end-diastolic left ventricular pressure ($r = 0.00$, P

TABLE III

Correlations Between Structural and Hemodynamic Findings Before Operation

	Number of Observations	Correlation Coefficient	*P* Value
Diameter* vs EDP	16	0.63	<0.01
Diameter vs MLAP	16	0.58	<0.05
Diameter vs h_D	16	0.80	<0.001
Diameter vs K_A	16	0.56	<0.05
Diameter vs E_m	16	0.53	<0.05
% fibrosis vs EDP	22	0.00	NS
% fibrosis vs MLAP	21	0.15	NS
% fibrosis vs h_D	22	0.29	NS
% fibrosis vs K_A	22	0.05	NS
% fibrosis vs E_m	22	0.09	NS

*Myocardial cell diameter (μ).

EDP = end-diastolic pressure (mm Hg); E_m = elastic stiffness (dynes·10^5/cm^2); h_D = end-diastolic wall thickness; K_A = stiffness constant; MLAP = mean left atrial pressure (mm Hg); NS = not significant (probability [*P*] > 0.05).

>0.05), mean left atrial pressure (r = 0.15, P >0.05), end-diastolic wall thickness (r = 0.29, P >0.05), stiffness constant K_A (r = 0.05, P >0.05) and elastic stiffness E_m (r = 0.09, P >0.05). Figure 4 shows the relation between percent fibrosis and the stiffness constant K_A. The stiffness constant is not influenced by the degree of fibrosis. Fibrosis was not different among the various types of overload (P >0.05) but K_A was significantly different among the three groups (aortic stenosis versus aortic insufficiency P <0.001, aortic stenosis versus mixed valve disease P >0.05 and mixed valve disease versus aortic insufficiency P <0.001).

Effect of corrective surgery on diastolic properties of the hypertrophied left ventricle (Table II): *Before operation,* end-diastolic left ventricular pressure and mean left atrial pressure were significantly elevated

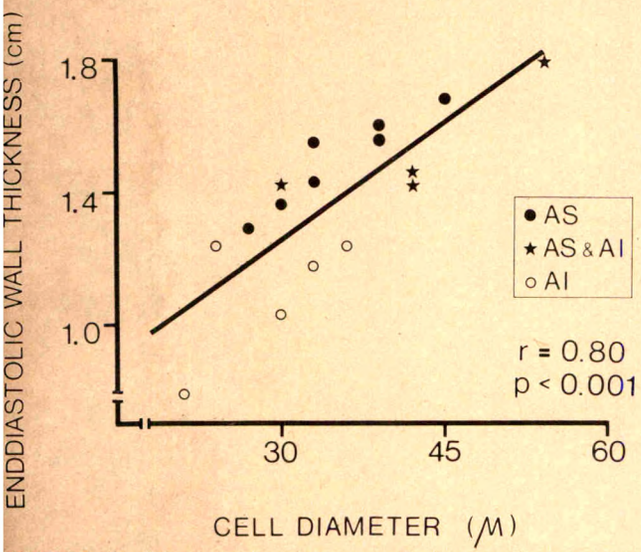


FIGURE 3. Significant relation between cell diameter (in microns) measured with morphometry, and end-diastolic wall thickness (in centimeters) of the left ventricle, determined angiographically. p = probability; other abbreviations as in Figure 1.

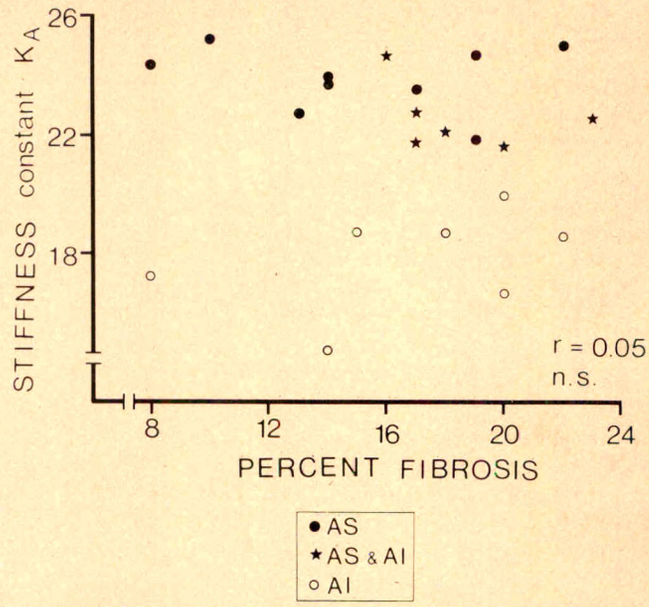


FIGURE 4. Lack of correlation between percentage fibrosis, measured with morphometry, and stiffness constant K_A, calculated as described in methods. n.s. = not significant; other abbreviations as in Figure 1.

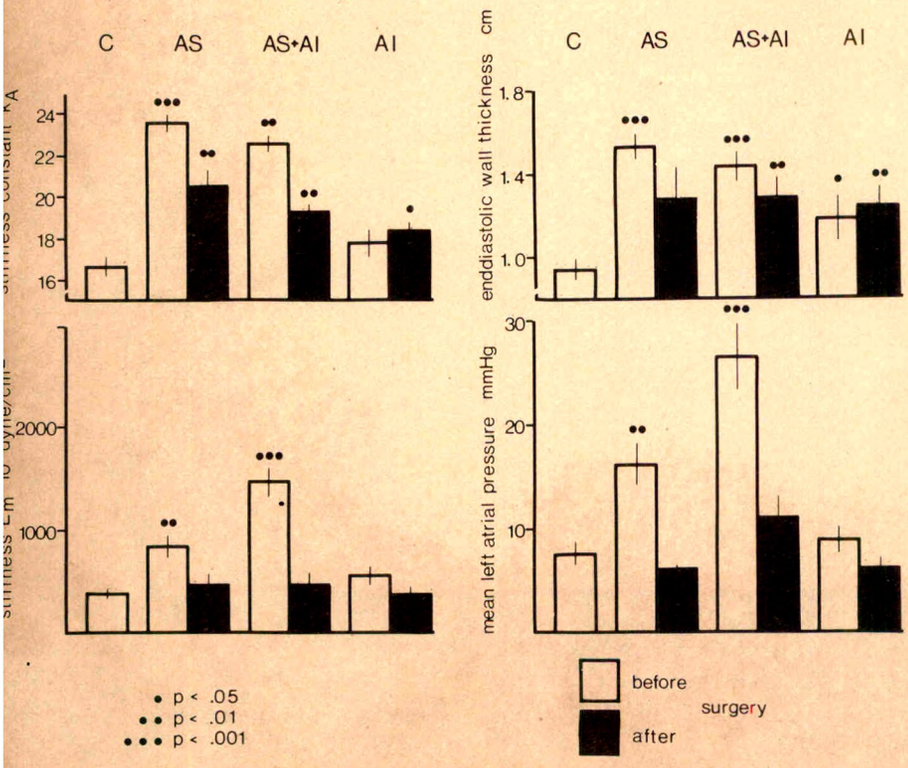


FIGURE 5. Preoperative (**white columns**) and postoperative (**black columns**) mean values ± standard error of the mean of stiffness constant K_A (**upper left panel**), elastic stiffness E_m (**lower left panel**), end-diastolic wall thickness (**upper right panel**) and mean left atrial pressure (**lower right panel**). After operation all parameters decrease. While stiffness constant and end-diastolic wall thickness remain moderately elevated, the elastic stiffness and mean left atrial pressure reach normal levels. C = control group. Other abbreviations as in Figure 1.

in patients with aortic stenosis and in those with mixed aortic valve disease but not in those with aortic insufficiency. End-diastolic volume was increased in patients with mixed aortic valve disease and in those with aortic insufficiency but not in those with aortic stenosis. End-diastolic wall thickness was significantly increased in all three groups of overload. Stiffness constant K_A and elastic stiffness E_m were significantly increased in patients with aortic stenosis and mixed aortic valve disease, but not in those with aortic insufficiency (Fig. 5).

Aortic valve replacement produced a decrease in end-diastolic and mean left atrial pressures. End-diastolic volume decreased significantly in all three groups. End-diastolic wall thickness and K_A decreased significantly after operation in patients with aortic stenosis and in those with mixed aortic valve disease but remained unchanged in those with aortic insufficiency. Elastic stiffness E_m decreased in all groups, but the decrease was significant only in patients with mixed aortic valve disease.

The following variables normalized completely after operation: end-diastolic left ventricular pressure (except in aortic stenosis), mean left atrial pressure, end-diastolic volume and elastic stiffness of the chamber (Fig. 5). End-diastolic wall thickness and stiffness constant K_A regressed only incompletely (Fig. 5). Close correlations were found between stiffness constant K_A and end-diastolic wall thickness ($r = 0.78$, Fig. 6) and between elastic stiffness E_m and mean left atrial pressure ($r = 0.85$, Fig. 7).

Heart rate before and after operation, respectively, was 81.0 ± 13.0 and 80.4 ± 7.3 beats/min in aortic stenosis, 88.4 ± 12.8 and 81.8 ± 7.0 in mixed aortic valve disease and 80.3 ± 17.2 and 84.7 ± 14.8 in aortic insufficiency. Paired comparison revealed no significant changes ($P > 0.05$). Mean aortic pressure before and after operation was 99.2 ± 14.4 and 94.6 ± 6.2 mm Hg in aortic stenosis, 81.9 ± 12.1 and 106.8 ± 11.5 mm Hg in mixed aortic valve disease and 101.9 ± 7.9 and 108.0 ± 18.5 mm Hg in aortic insufficiency. Comparison of paired data showed no change in aortic stenosis or aortic insufficiency but a significant increase in mixed aortic valve disease ($P < 0.01$).

Preoperative systolic ejection fraction was depressed in patients with aortic stenosis (56.8 ± 9.3 percent versus 69.9 ± 5.3 percent in control subjects, $P < 0.01$), in patients with mixed aortic valve disease (36.6 ± 15.6 percent, $P < 0.001$) and in patients with aortic insufficiency (54.3 ± 7.0 percent, $P < 0.001$). After operation, ejection fraction increased in aortic stenosis (to 77.0 ± 6.9 percent, $P > 0.05$), in mixed aortic valve disease (to 65.8 ± 4.2 percent, $P < 0.05$) and in aortic insufficiency (to 63.0 ± 6.6 percent, $P < 0.05$). The postoperative ejection fraction in all three groups did not differ from the value in the normal control group ($P > 0.05$).

Discussion

Limitations of analysis: We measured myocardial cell diameter in hypertrophied hearts from biopsy specimens obtained at the time of open heart surgery. Transmural biopsy tissues were taken from all patients and were analyzed with usual morphometric techniques.[17] It is believed that a biopsy specimen is representative of the hypertrophied myocardium because adaptive left ventricular hypertrophy is homogeneously

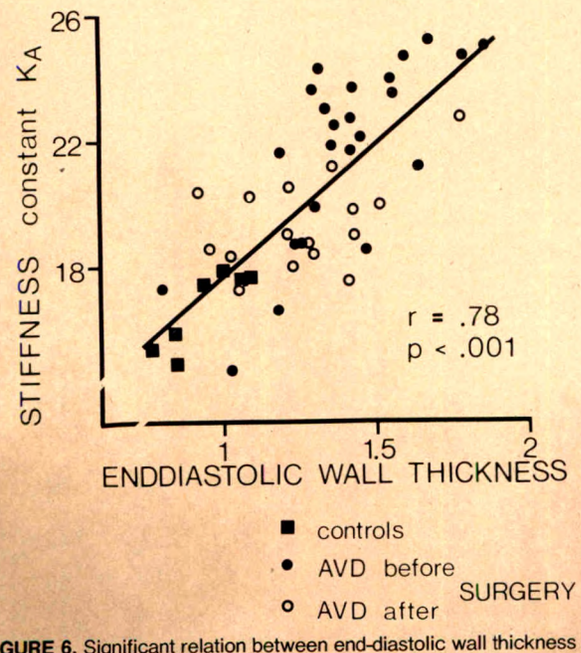


FIGURE 6. Significant relation between end-diastolic wall thickness and stiffness constant K_a. AVD = aortic valve disease; p = probability.

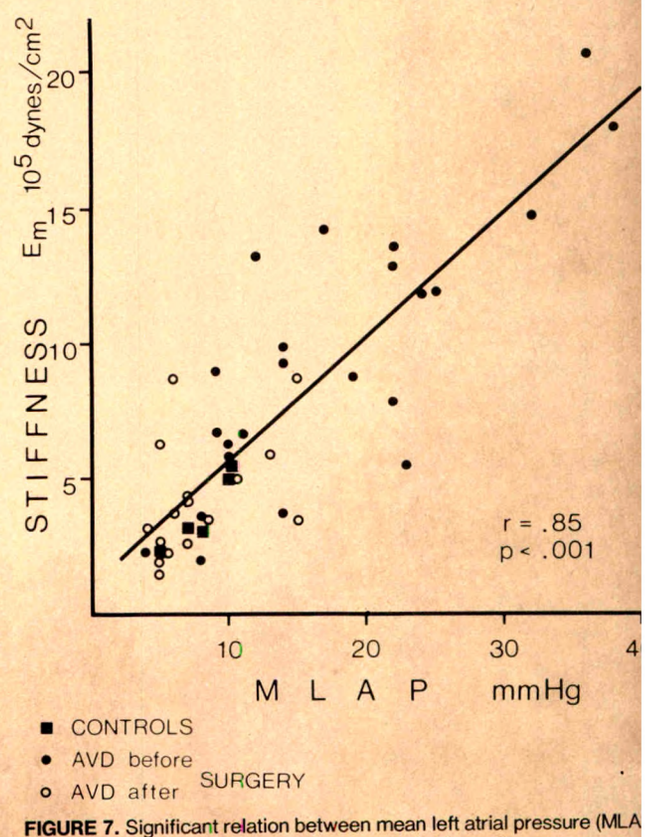


FIGURE 7. Significant relation between mean left atrial pressure (MLA and elastic stiffness E_m. Abbreviations as in Figure 6.

distributed and not localized.[18] Because cell diameter may vary within the same section we averaged the results of at least 30 individual measurements in each patient. This transmural biopsy technique, performed under direct vision, was previously used in patients with coronary artery disease,[19] and the data obtained were found to be of considerable accuracy when compared with electrocardiographic and ventriculographic findings from the same region. However, in the present study we compared data from an isolated sample with the diastolic properties of the whole heart, thus allowing only rough correlations.

Left ventricular diastolic properties were evaluated using the method introduced by Mirsky and Parmley.[16] This calculation is based on the simple empirically derived pressure-volume relation developed by Gaasch et al.[20] Evaluation of muscle and chamber stiffness in patients with a wide range of end-diastolic volumes and pressures remains an important clinical problem. When diastolic volumes and pressures of our patients were plotted over the entire diastolic period it was not possible to compare different ventricles because the pressure and volume data did not overlap, as would be needed for comparison. Mirsky and Parmley[16] proposed an alternative approach to this problem, utilizing the stress-strain relation for an elastic material. This concept allows comparisons to be made between elastic structures of different sizes and shapes.[21]

The elastic stiffness of the mid wall was approximated in our analysis using the following assumptions and limitations: (1) Ventricular geometry was assumed to be spherical. (2) Instantaneous mid wall stress was assumed to be representative of the average fiber stress, the ventricular wall material behaving as a homogeneous elastic medium. Mirsky et al.[22] found that the measurements of elastic stiffness based on spherical geometry always underestimate the wall stiffness by comparison with measurements based on ellipsoidal geometry. However, the qualitative results were unchanged as demonstrated by an excellent correlation between both methods. The second assumption represents a real limitation because pressure-fiber length curves have been shown[23] to vary for the inner, mid wall and outer fibers and also from the apex to the base. Therefore, the model used can only approximate global values of wall stiffness and does not quantitate stiffness of different regions.

Our results show that the stiffness constant K_A correlates closely with the end-diastolic wall thickness. Furthermore, the clinically more important elastic stiffness of the chamber (E_m), representing resistance to ventricular filling, correlates closely with mean left atrial pressure when preoperative and postoperative values are considered. These relations are interpreted as empirical justification for the elasticity theory used. It must be noted that isolated reduction of end-diastolic volume after operation does not induce a significant decrease in the stiffness constant K_A. Thus, in our group with aortic insufficiency, end-diastolic volume decreased from 168 to 98 ml/m^2, but K_A remained essentially unchanged (17.8 versus 18.4). We suggest that a simple measurement of mean left atrial pressure can be taken as a rough approximation of elastic stiffness of the left ventricular chamber.

Relation between myocardial structure and diastolic properties of the hypertrophied left ventricle: End-diastolic wall thickness increases as a result of growth of cell diameter in chronically overloaded hearts. The diameter of myocardial cells is larger in pressure-overloaded hearts than in volume-overloaded hearts. In the hearts with pressure overload there was a linear relation between cell diameter and end-diastolic wall thickness, suggesting that the severity of pressure overload is reflected by the cell diameter of the tissue specimen. This relation is well known from postmortem studies[24] and confirms that the technique we used for histologic evaluation is valid within a fair range of accuracy. The myocardial cell diameter was a major determinant of preoperative end-diastolic stiffness, end-diastolic pressure and mean left atrial pressure. These results extend the findings of earlier studies[25–27] which demonstrated that end-diastolic wall thickness is a determinant of diastolic behavior of the left ventricle.

An important finding is that myocardial fibrosis does not directly influence the diastolic properties of the left ventricle in chronic aortic valve disease. Several studies have documented that fibrosis develops in chronic left ventricular hypertrophy,[18,24] probably as a consequence of decreasing capillary fiber ratio.[28] It has been speculated that the increased stiffness of the overloaded heart may be due to increased connective tissue content of the myocardium.[3,21] Our results do not confirm this assumption. The complete reversibility of chamber stiffness after operation also shows that myocardial fibrotic content in the hypertrophied heart has no major effect on the diastolic properties of the left ventricle. The influence of myocardial fibrosis on cardiac function was recently evaluated in patients with mitral incompetence, and it was concluded that the connective tissue content of the myocardium is related to clinical symptoms in these patients.[29] In contrast, comparison of angiographic and postmortem evaluation of the myocardium in patients with a hypertrophied heart due to valvular heart disease showed that left ventricular contractile function may be severely depressed even in the absence of significant fibrosis.[30] This is indirect evidence that other causes, such as degenerative ultrastructural myocardial alterations, may play a role in the impairment of contractile function in chronic valvular heart disease.[31–33]

Effect of corrective surgery on diastolic properties of the hypertrophied left ventricle: Reversibility of hypertrophy has been the focus of attention in recent animal studies,[5,6] that demonstrated partial or complete reversibility of diastolic "functional compliance" after correction of volume overload. This reversibility was accompanied by a significant regression of hypertrophy. In children with ventricular septal defect a considerable regression of hypertrophy was described.[34] We found a significant reduction of end-diastolic wall thickness and end-diastolic volume in pressure-overloaded hearts representing regression of

hypertrophy. In volume-overloaded hearts end-diastolic volume decreased, but end-diastolic wall thickness remained unchanged. End-diastolic pressure, mean left atrial pressure and elastic stiffness normalized in most cases, whereas stiffness constant and end-diastolic wall thickness remained moderately elevated after operation.

Clinical implications: The most important finding of our study is the reduction and normalization of both elastic stiffness of the left ventricle and mean left atrial pressure in most patients after operation for aortic valv disease, thus explaining the alleviation of clinica symptoms. Aortic valve replacement with a Björk Shiley prosthesis normalized diastolic cardiac functio and revealed a great adaptive power of the hypertro phied myocardium. The failure of previous studies[4] t demonstrate improvement in left ventricular diastoli function may be related to the valve model used: Th Starr-Edwards prosthesis produces greater outflo tract obstruction than the Björk-Shiley valve.[35]

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Localization of Pericardial Effusion with Wide Angle Phased Array Echocardiography

RANDOLPH P. MARTIN, MD*
HARRY RAKOWSKI, MD
JAMES FRENCH, MD, FACC
RICHARD L. POPP, MD, FACC

Stanford, California

Twenty-eight patients with proved pericardial effusions were studied in the left lateral decubitus position with an 80° phased array sector scanner to determine the distribution of pericardial effusions of various sizes. Twenty-one of 28 patients were studied 2 minutes after assuming the sitting position to determine the change in the distribution of the effusions with postural change. In small volume effusions, the fluid was truly posterior at and below the atrioventricular groove. With moderate-sized effusions a more uniform distribution of the fluid was found, and with large effusions more fluid was visualized apically, posteromedially, laterally and anteriorly. Upright redistribution of the fluid was seen with moderate to large nonloculated effusions. Assumption of a uniform distribution of pericardial effusion used for M mode quantification is most valid for moderate effusions and less valid for small and large effusions. Imaging was performed in two additional patients with cardiac tamponade to assess qualitative changes in short axis ventricular volumes with respiration. The introduction of a pericardiocentesis needle was visualized. Clinical implications are discussed.

In the years since Feigenbaum's original application,[1] echocardiography has proved a clinically useful noninvasive method for the diagnosis of pericardial effusion. Recent work from our laboratory[2] has established M mode echocardiography as a sensitive technique for detecting small volumes of pericardial fluid. Horowitz et al.[2] proposed a spheroid model of the pericardium and heart for quantitating the volume of pericardial effusion based on the assumption of a uniform distribution of the fluid in the pericardial space: In such a model the pericardial volume is the difference in the cubed end-diastolic diameters of the pericardium and heart. However, the validity of the assumed uniform distribution of fluid has not been tested over a wide range of absolute volumes.

Two dimensional wide angle phased array echocardiography has proved to be an exciting new technique.[3] It offers dynamic images of the heart in multiple cross-sectional planes, allowing for simultaneous visualization of the entire left ventricle and surrounding structures throughout the cardiac cycle. This technique obviously overcomes the lack of spatial orientation inherent in conventional M mode echocardiography. The narrow field of the M mode echocardiogram has led to pitfalls in the diagnosis of pericardial effusion, secondary to interpretive problems with pleural effusion, medial transducer angulation, calcified mitral anulus and enlarged left atrium.[4–7]

The specific purposes of this study were (1) to explore the echocardiographic anatomy of the pericardial space as visualized with this two-dimensional system, (2) to determine the distribution and effect of postural change on distribution of various-sized effusions relative to the heart, and (3) thereby investigate the basic assumption on which single-dimensional quantification is based. Additionally, two patients with clinical evidence of cardiac tamponade were studied to assess qualitative changes in the short axis ventricular volume with respiration. One of these two patients was studied during therapeutic and diagnostic pericardiocentesis.

rom the Division of Cardiology, Stanford Uniersity School of Medicine, Stanford, California.
his work was supported in part by Grant HL-5866 om the National Institutes of Health, Bethesda, laryland. Manuscript received April 25, 1978; evised manuscript received July 18, 1978, accepted July 19, 1978.
**Present address and address for reprints: andolph P. Martin, MD, Cardiology Division, niversity of Virginia Medical School, Charttesville, Virginia 22901.

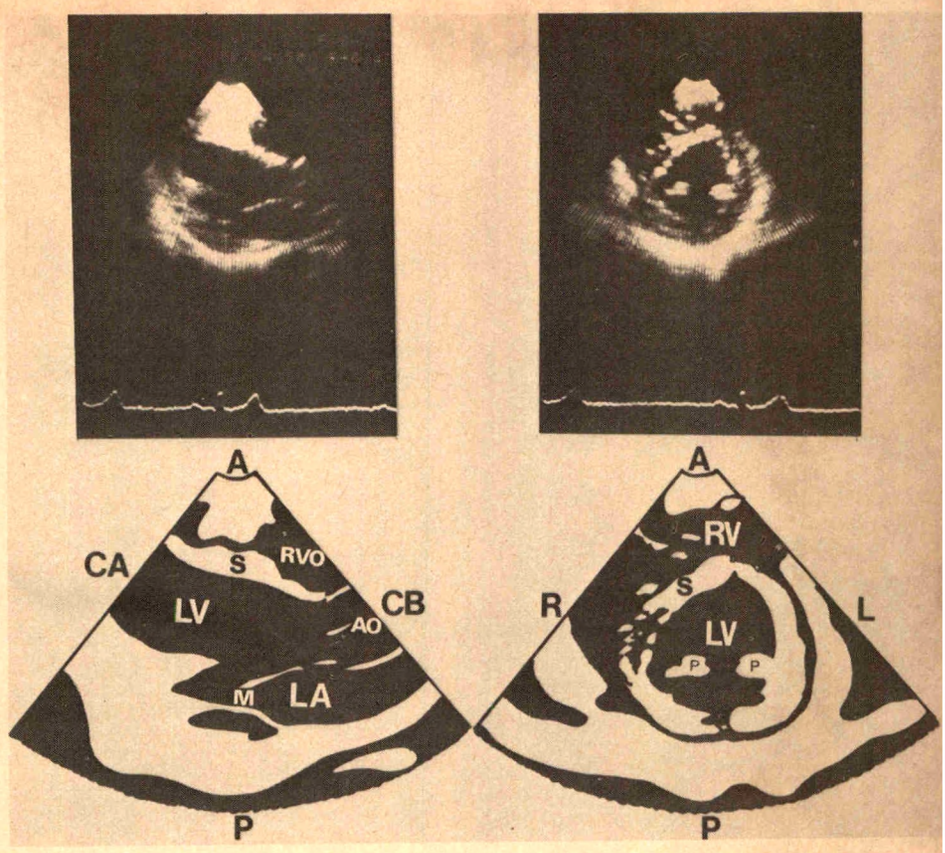


FIGURE 1. Normal subject, long and short axis views. **Left panel,** a left ventricular long axis stop-frame image and schematic diagram at end-diastole. No pericardial effusion is seen posterior to the posterobasal segment of the left ventricular wall. **Right panel,** stop-frame image and schematic drawing of the left ventricle in short axis view at the level of the papillary muscles (p). The full thickness of the left ventricular myocardium can be seen, and no pericardial effusion is present. A = anterior; AO = aorta; CA = cardiac apex; CB = cardiac base; L = left; LA = left atrium; LV = left ventricle; M = mitral leaflets; P = posterior; p = papillary muscles; R = right; RV = right ventricle; RVO = right ventricular outflow tract; S = interventricular septum.

Methods

Patient selection: Twenty-eight normal healthy subjects were selected as reference standards on the basis of high quality one- and two-dimensional echocardiographic studies. Twenty-eight patients who met our laboratory's echocardiographic criteria of pericardial effusion were selected on the basis of high quality one-dimensional echocardiographic studies.[8] These patients ranged in age from 6 to 70 years and had various causes for their pericardial effusion. Subsequent confirmation of the presence of pericardial effusion was obtained at the time of pericardiocentesis or cardiac surgery, or both, or on the basis of the clinical setting (radiation therapy, renal failure, for example) plus a change in cardiac silhouette in the chest X-ray film. Two additional patients with clinical evidence of cardiac tamponade also were selected on the basis of high quality single-dimensional echocardiographic studies.

Echocardiographic methods—equipment: *All one-dimensional echocardiograms* were performed using a Smith Kline Ekoline 20A ultrasonoscope and a 2.25 megahertz transducer collimated to 7.5 cm and pulsed with a repetition rate of 1,000/sec. The echocardiograms were recorded on an Irex 101 or Ekoline 21 strip chart recorder. The technique of M mode scanning ultrasonic examination has previously been described.[9,10] The M mode echocardiograms were assessed by at least two observers. The method for quantifying pericardial effusion described by Horowitz et al.[2] was used.

Two-dimensional echocardiographic studies were obtained with a phased array sector scanner developed at the Varian Associates Corporate Research Laboratories and undergoing clinical evaluation in the Stanford University Cardiology Division. This imaging system uses a hand-held 32 element 2.25 megahertz transducer array that measures 1.3 by 1.2 cm at the site of skin contact and relies on the phased array principle to steer the sound beam through a pie slice-shaped sector of a circular plane.[11] Images are presented in a dynamic format. The field of view is 80° in an azimuthal direction and 21 cm in depth; there are 30 image frames/sec, each consisting of 66 lines of information. Azimuthal resolution ranges from 2 to 5 mm within the field of view, range resolution from 1.5 to 2 mm. This system differs from the two-dimensional phased array system previously described by von Ramm and Thurstone,[12] which has a dynamic focus during the transmitting and receiving periods rather than a fixed acoustic focus.

Images are recorded on 1 inch (2.54 cm) reel to reel video tape for later playback and review. Analysis can be performed during playback at real-time speed, slow motion speed and with stop action. Single frame photographs of the video monitor, as shown in this study, were made with a Polaroid® camera. Such static images are degraded optically because stop-action pictures show only a single field of a complete two field video frame. Equally important is the loss of visual integration of motion that normally occurs as one views dynamic recordings.

Study procedure: The examination procedure was similar to that previously described by Kisslo et al.[3] The transducer initially was oriented so that the viewed plane was parallel with the long axis of the left ventricle. Short axis images were obtained by turning the transducer 90° clockwise. To record a short axis sweep from the level of the aorta and left atrium toward the apex of the left ventricle, the transducer is held at a fixed locus on the chest wall while tilted cephalad toward the aorta, and then gradually swept caudally toward the cardiac apex, similar to the method for obtaining an M mode sweep. The derived images are presented as if one were viewing the heart from the foot of the patient's bed. Representative long and short images of a normal subject are shown in Figure 1. Additionally the transducer was often placed over the cardiac

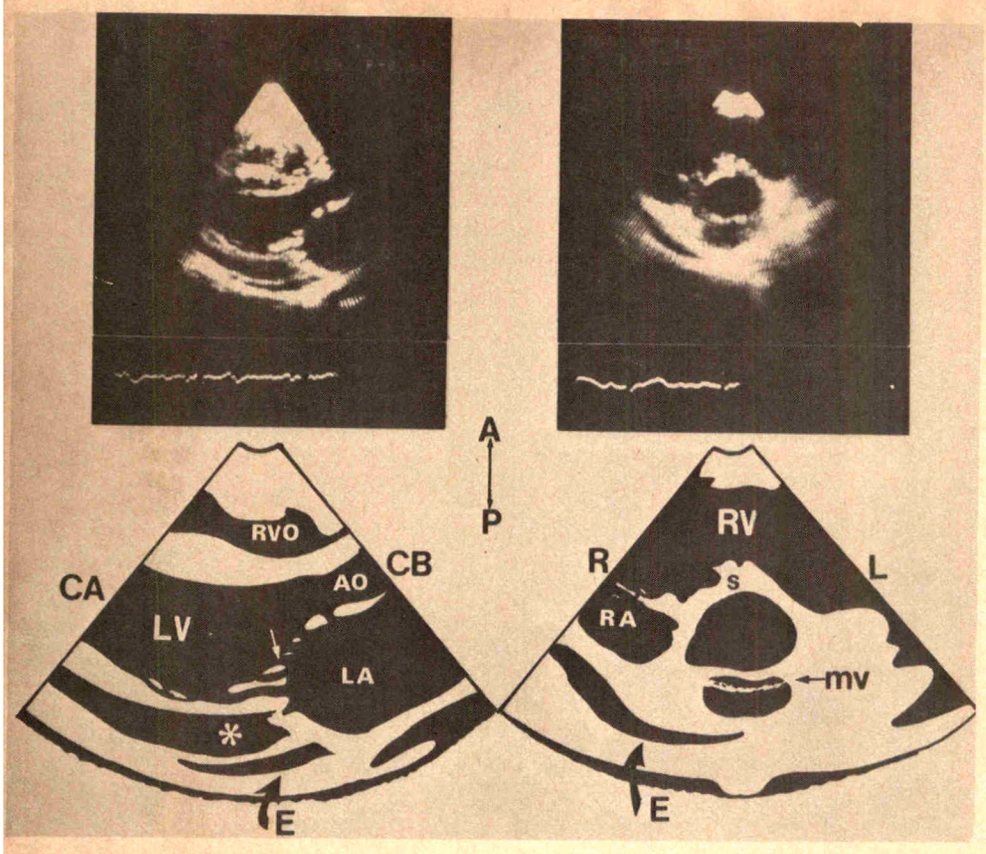


FIGURE 2. Small pericardial effusion: long and short axis views. **Left panel,** a long axis stop-frame image of the left ventricle with schematic diagram. The small pericardial effusion (E) can easily be identified posteriorly and distal to the area of the atrioventricular (A-V) groove. The **asterisk** marks the posterobasal left ventricular wall. The **small white arrow** points to the free edge of the mitral valve. **Right panel,** a short axis stop-frame image and schematic diagram at the level of the A-V groove and mitral valve (mv). The small pericardial effusion is again identified lying posterior and medial to the A-V groove. RA = right atrium; other abbreviations as in Figure 1.

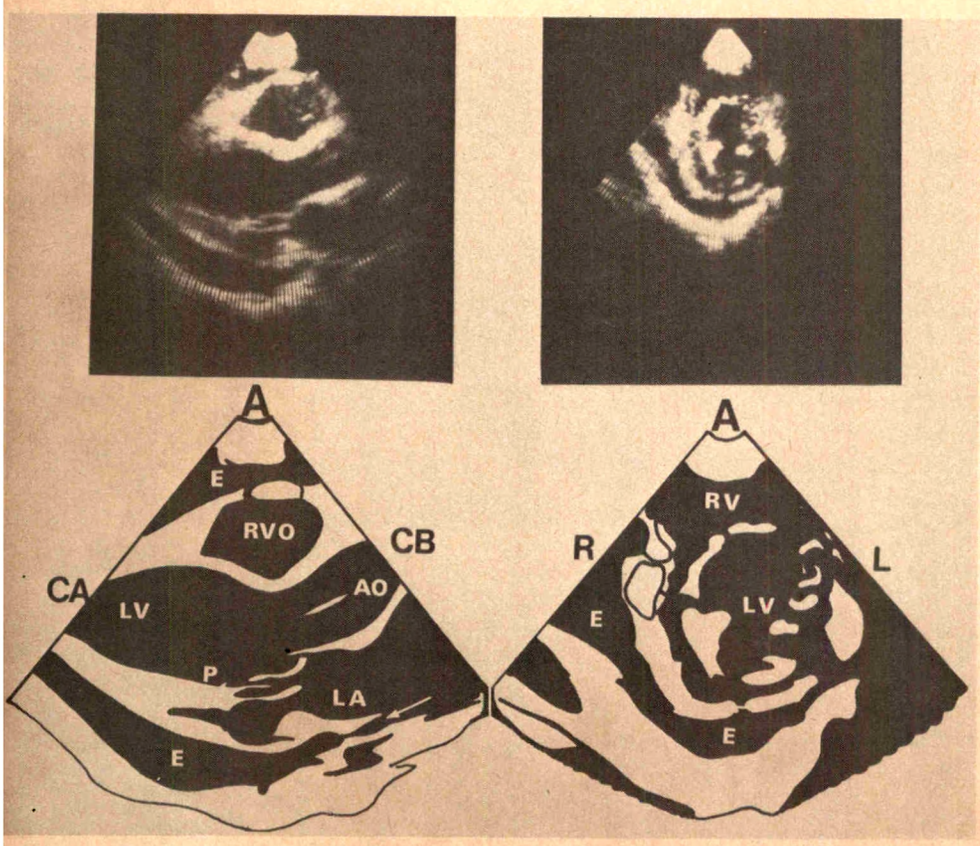


FIGURE 3. Moderate pericardial effusion, long and short axis views. **Left panel,** a left ventricular stop-frame image and schematic diagram in a patient with a moderate-sized pericardial effusion (E). The pericardial effusion is layered more evenly around the left and right ventricles as viewed in the long axis orientation. The effusion is seen not only posteriorly, but also out toward the apical region and anterior to the right ventricular outflow tract. The **small white arrow** points to the presence of the effusion behind the left atrial wall in the area of the oblique sinus. **Right panel,** a stop-frame image and schematic diagram of the left ventricle at the level of the papillary muscle-chordae tendineae junction. The moderate pericardial effusion can be seen to be more evenly distributed not only posteriorly, but medially as well. Abbreviations as in Figure 1.

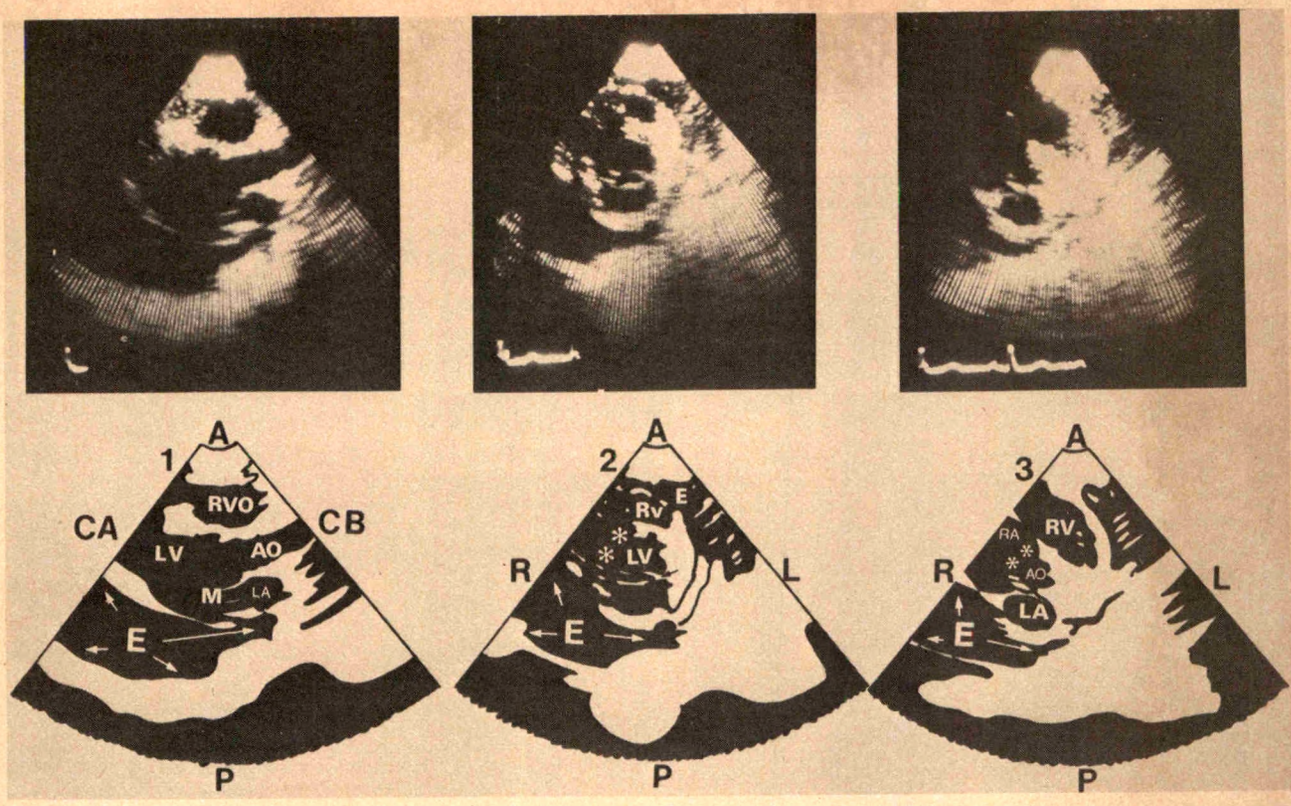


FIGURE 4. Large pericardial effusion. **Panel 1,** a left ventricular stop-frame image and schematic diagram in a patient with a large pericardial effusion (E). In contrast with the moderate effusion, the large effusion visualized in this patient not only extends behind the left atrium **(long white arrow)** but also distributes itself apically **(small white arrows). Panel 2,** a short axis stop-frame image and schematic diagram of the right and left ventricles in the same patient at the level of the mitral valve orifice **(small black arrow).** The large collection of pericardial fluid can be seen to surround the left and right ventricular chambers; a major distribution lies posteriorly and medially **(small white arrows).** The **asterisks** mark the continuation of the interventricular septum, which is not visualized in this stop-frame image. The effusion (E) can be seen anteriorly as well. **Panel 3,** a stop-frame short axis image and schematic diagram of the same patient at the level of the aorta (AO) and left atrium (LA). The effusion is clearly seen behind the left and right atria, as shown by the **small white arrows.** The **asterisks** complete the medial aspect of the aortic wall, which is no longer visualized in this stop-frame image. RA = right atrium; other abbreviations as in Figure 1.

apex and the image derived in both long axis and short axis format as described.

All patients were studied at rest in a 30° left lateral decubitus position with the head elevated. Repeat studies were performed 2 or more minutes after the patients assumed the sitting position. The two patients with cardiac tamponade were studied in the supine left lateral decubitus position, and special care was taken to image the heart in short axis at the level of the mitral apparatus throughout multiple respiratory cycles. One of these two patients was studied in the supine, 30° left lateral decubitus and sitting positions during diagnostic pericardiocentesis. An attempt was made to visualize the introduction of a needle into the pericardial sac.

Specific attention was focused on the echocardiographic anatomy of the pericardial space and on distribution of various-sized effusions around the left ventricle and left atrium and anterior to the right ventricle as visualized with this system. In the patients with cardiac tamponade we qualitatively compared the sizes of the right and left ventricles during inspiration and expiration. An automated M mode cursor that can be selectively steered throughout the sector arc to any desired position was used to draw off a simultaneous M mode echocardiogram from the tip of the mitral valve apparatus and minor axis of the left ventricle. Expiratory and inspiratory measurements of the mitral valve E-Fo slope, diastolic amplitude of anterior mitral valve excursion, and left and right ventricular end-diastolic internal dimensions were made in both patients.

Results

One dimensional studies: Long and short ventricular axis two dimensional studies were graded as excellent or good in all 28 patients in the resting supine and the resting left lateral decubitus positions. Good two dimensional images were also obtained in 21 of the 28 patients after 2 minutes of sitting. In all normal subjects, pericardial effusion was absent on both one and two dimensional studies. The one dimensional studies in all 28 patients showed an echo-free space that persisted throughout the cardiac cycle between the posterior epicardium and a poorly moving pericardium. This is pattern D, as suggested by Horowitz et al.,[2] who found that this pattern was associated with at least 100 ml or more of pericardial effusion. Additionally, the one dimensional studies were used to classify the patient into those with small (less than 100 cc), moderate (10

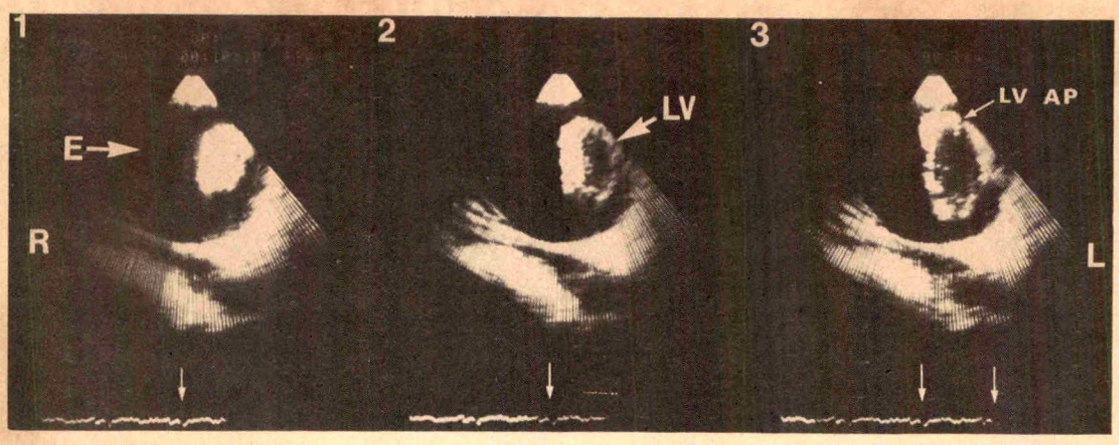


FIGURE 5. Large pericardial effusion visualized at the cardiac apex. These three panels are sequential views taken throughout one cardiac cycle with the transducer placed stationary over the cardiac apex. The plane of the beam is perpendicular to the interventricular septum in a 90° clockwise fashion. The **thin white arrow** over the electrocardiogram signifies the R wave of the same QRS complex. **Panel 1,** an early diastolic short axis view with the echographic beam just intersecting the apical myocardial wall. The majority of the imaged apical region is taken up by the very large apical pericardial effusion, as shown by the thick **white arrow** (E). **Panel 2,** a later diastolic view revealing that a larger portion of the left ventricle (LV) and left ventricular cavity has rotated through the intersecting sector beam. **Panel 3,** the final end-diastolic sequence revealing the largest portion of the left ventricle to have moved through the intersecting beam. The left ventricular apex (LV AP) is closest to the transducer and the cardiac base is farthest from the transducer. These three sequential views show that in the presence of a large pericardial effusion that distends the apical pericardial recesses, the ultrasonic beam can be angled so that the left ventricular apex can be seen to swing into and out of the plane of the beam. Abbreviations as in Figure 1.

cc to 500 cc) and large (greater than 500 cc) pericardial effusions on the basis of an assumed uniform distribution and cubed volume method of Horowitz et al.[2] Accordingly, there were 6 patients who had a small pericardial effusion, 11 with a moderate effusion and 11 with a large effusion.

Two dimensional studies: The presence of pericardial effusion was easily identified in all 28 patients with the two dimensional echocardiographic studies. The 80° long and short axis left ventricular views showed clear definition of pericardial space. The pericardium was identified by altering transmitted power as in the M mode technique. In all patients, but especially in those with a moderate to large pericardial effusion, the two dimensional studies demonstrated pericardial attachment to the left atrium cephalad to the atrioventricular (A-V) groove. The distribution of the pericardial effusion in the recumbent position was found to vary with the amount of fluid present.

In patients with a small pericardial effusion, the fluid was at and below the A-V groove, with minimal or no fluid apically, laterally or anteriorly. Two of the six patients with a small effusion also had an anterior space containing a homogeneous pattern of echoes between the chest wall and the anterior right ventricular wall which was shown, with appropriate damping settings, not to be a pericardial effusion. Figure 2 shows a stop-frame photograph taken from one of the patients with a small pericardial effusion.

With moderate-sized effusions there was continued predominant posterior localization of the fluid near the A-V groove but also a trend toward more even distribution of the fluid apically, medially and anteriorly (Fig. 3). In all 11 patients with a moderate-sized effusion there was some echo-free pericardial space cephalad to the posterior A-V groove. None of these patients exhibited excessive motion of the heart within the pericardial sac.

In large effusions, the additional fluid was found equally posteromedially and also apically, laterally and anteriorly. There was proportionately less expansion of the posterior space near the area usually visualized with one dimensional echocardiography (Fig. 4). All 11 of these patients had some echo-free space cephalad to the A-V groove behind the left atrium. In 5 of these 11 patients, the posterior left atrial wall had an unusual systolic anterior excursion, and in 4 patients the entire heart oscillated markedly within the large pericardial effusion. With the transducer placed over the cardiac apex and the beam oriented from the right hip to the left shoulder, a view of the effusion in the pericardial space and motion of the heart within this large effusion was easily recorded in these four patients. By angling the transducer so that the beam just intercepted the pericardial space and effusion, the left ventricular apex could be seen to swing into and out of the plane of the beam (Fig. 5).

In 3 of the 11 patients with a large pericardial effusion, the anterior right heart wall near the right ventricular outflow tract showed marked excursion, virtually invaginating during early diastole (Fig. 6). Redistribution of the fluid toward the apex when the patient was upright was appreciated only in patients with moderate and large effusions (Fig. 7).

In the two patients with cardiac tamponade there was a qualitative inspiratory increase in right ventricular dimensions, with a simultaneous decrease in left ventricular dimensions, in addition to a slight shift in cardiac position within the pericardium. Simultaneous M mode recordings revealed an expiratory to inspira-

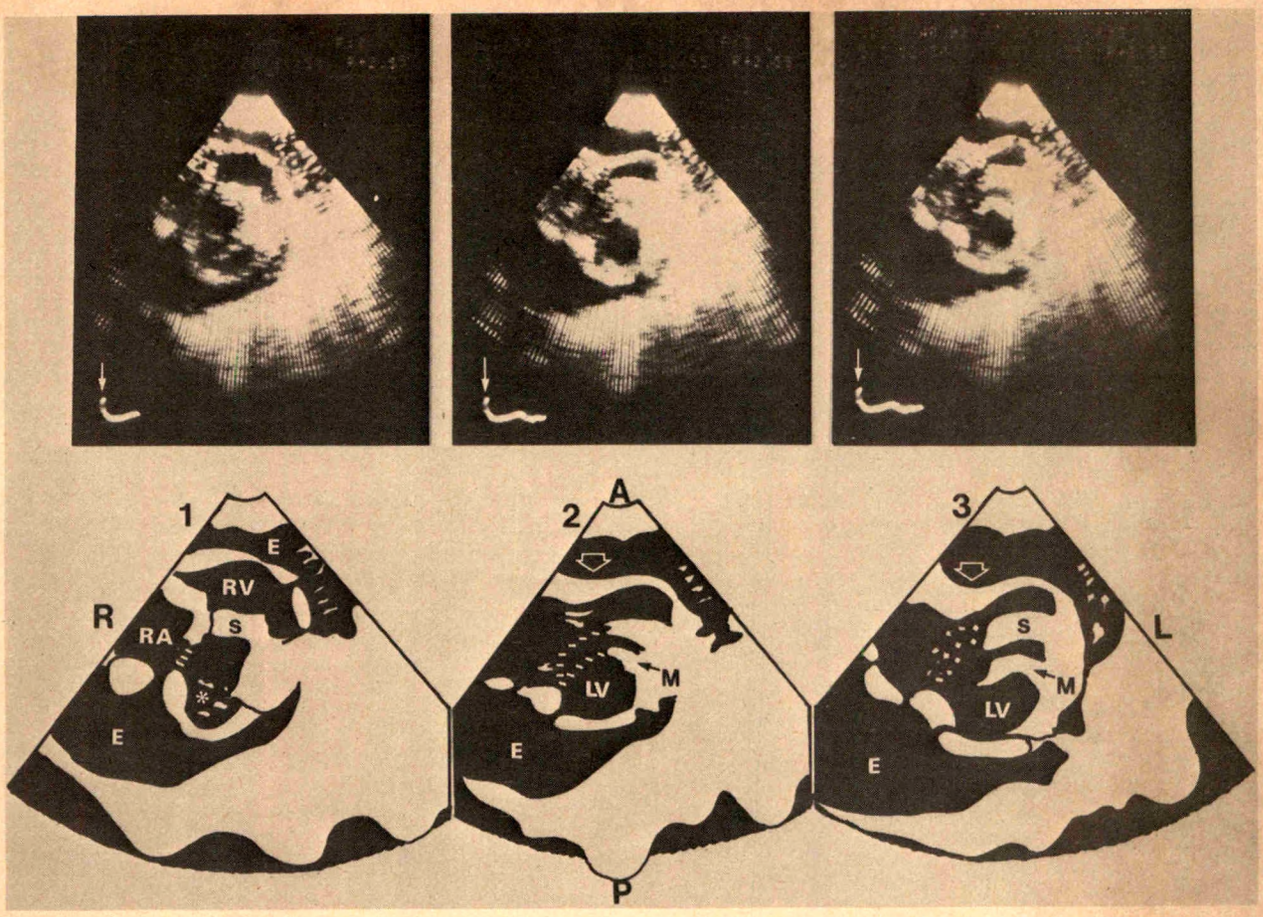


FIGURE 6. Stop-frame sequential short axis images and schematic diagrams of the right and left ventricle at the level of the mitral valve apparatus in a patient with a large pericardial effusion. The **small white arrow** in each panel marks the same R wave of the QRS complex. **Panel 1,** a stop-frame short axis image of the left and right ventricles at end-systole. The **asterisk** marks the mitral valve orifice. The right ventricular cavity (RV) and right atrial cavity (RA) are clearly seen. The large pericardial effusion is seen to surround both the right and left ventricles; the major distribution lies posteriorly and medially. **Panel 2,** an early diastolic image with the transducer in the same location. The invagination of the anterior right ventricular wall **(large white arrow)** is clearly seen to compress the imaged right ventricular cavity. **Panel 3,** a later diastolic image showing the most marked invagination **(large white arrow)** of the anterior right ventricular wall. The very large pericardial effusion (E) is seen to surround both the right and left ventricles and to show a predominant posterior medial localization. M = anterior leaflet of the mitral valve; RA = right atrium; other abbreviations as in Figure 1.

tory decrease in (1) the mitral E-Fo slope (6.5 to 2.2 cm/sec), (2) diastolic anterior mitral valve excursion (4.4 to 2.2 cm), and (3) left ventricular end-diastolic internal dimension (4.6 to 3.6 cm); there was an expiratory to inspiratory increase in the right ventricular end-diastolic internal dimension (2.8 to 3.8 cm) in one patient. Similar findings were obtained from the second patient. One of these patients had a therapeutic pericardiocentesis during two dimensional imaging. We could visualize the pericardiocentesis needle in the apical pericardial recess. The ability to image the size and location of the pericardial effusion during the pericardiocentesis aided us in assessing the amount of fluid remaining as the pericardiocentesis progressed.

Discussion

A small anterior homogeneously echo-producing space between the chest wall and right ventricular wall was seen in one third of our patients with a small pericardial effusion. Multiple images in many planes suggested that this anterior echo-free space was not continuous with the pericardial space. This finding supports our experience that the existence of an anterior separation is significant for effusion only in the presence of a posterior echo-free space.[2] Whether this anterior space represents fibrous fascial tissue, adipose tissue or other material has yet to be proved.

Advantages in differential diagnosis: The ability of wide angle two dimensional echocardiography to identify accurately intracardiac and pericardial anatomy obviously offers a potential for reducing the pitfalls inherent in the diagnosis of pericardial effusion. Many authors[4–7] have pointed out the interpretive problems secondary to pleural effusion, medial transducer angulation, calcified mitral anulus and a large left atrium. The wide angle capability offered by phased array systems should obviate these problems. Pericardial effusion was not confused with either a calcified mitral an-

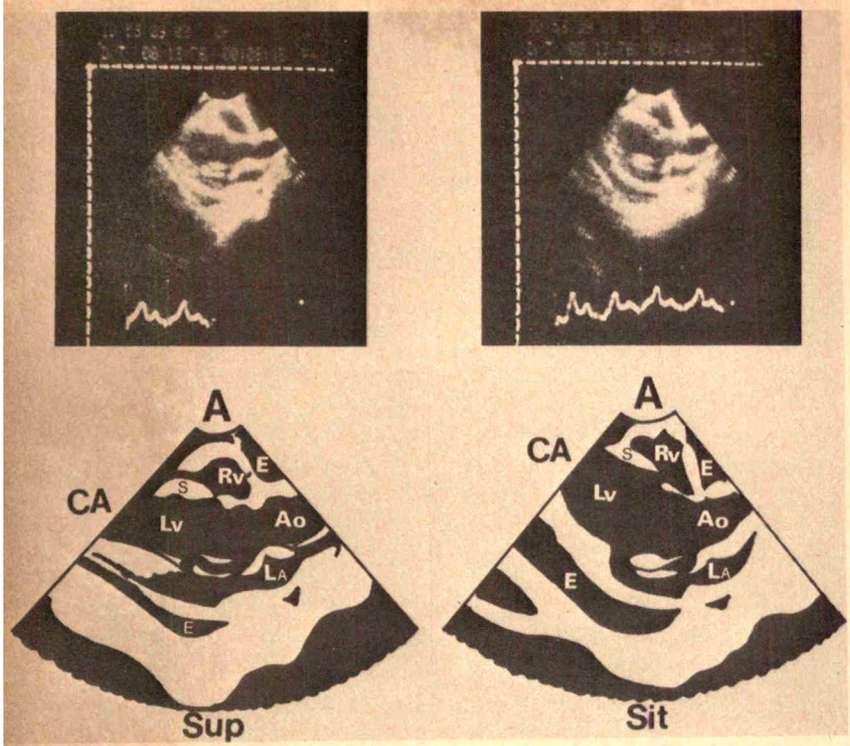


FIGURE 7. Redistribution of the pericardial effusion in the upright position. **Left panel,** a stop-frame left ventricular long axis image and schematic diagram from a patient with a moderate pericardial effusion. The pericardial effusion (E) is evenly distributed behind the imaged left ventricular walls and anterior to the right ventricle. This image is obtained with the patient in the standard supine (Sup) position. **Right panel,** a stop-frame left ventricular long axis image and schematic diagram in the same patient after 2 minutes of sitting. The image is obtained with the patient in the sitting (Sit) position. The pericardial effusion has assumed a more apical distribution (E). Abbreviations as in Figure 1.

ulus or pleural effusion in our patients (Fig. 8). We have subsequently studied three patients with a giant left atrium (secondary to long-standing mitral valve disease) who were thought to have a large pericardial effusion on the basis of M mode studies. Subsequent two dimensional studies revealed that the large left atrium and appendage wrapped around behind the left ventricle giving the appearance in the M mode echocardiogram of an echo-free space posterior to the left ventricle.

Distribution of pericardial effusions: In all six patients with a small pericardial effusion, the fluid appeared to be totally posterior at the diaphragmatic portion of the A-V groove, or apical to it. This localization of small pericardial effusions behind the left ventricular posterobasal myocardium is just slightly caudal to or at the site of the typical single dimensional left ventricular study. This probably accounts for the sensitivity of single dimensional echocardiography to detect small volume effusions, but in a small effusion one cannot assume that the fluid forms a uniform shell around the heart. Although moderate-sized effusions retained this prominent posterior localization, there was a more even distribution of the pericardial fluid anteriorly, apically and laterally. Moreover, in patients with a large pericardial effusion, the posteromedial and apical recesses of the pericardial sac contained a disproportionate amount of the fluid compared with the space behind the posterobasal left ventricular myocardium, the area usually visualized with single dimensional echocardiography.

Our findings of the volume distribution of various-sized pericardial effusions suggest that single dimen-

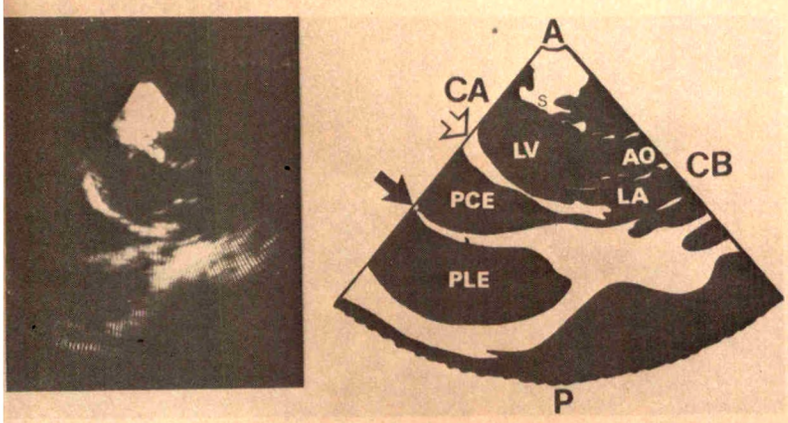


FIGURE 8. Large pericardial and pleural effusions. **Left,** a stop-frame left ventricular long axis image; **right,** a schematic diagram. The presence of a large pericardial effusion (PCE) is easily recognized. This effusion is predominantly in the apical recesses **(between the white and black arrows)** but can be seen to extend behind the left atrium. The pleural effusion (PLE) is easily distinguished from the pericardial effusion. The **large black arrow** marks the pericardial sac separating the pericardial from the pleural effusion. Abbreviations as in Figure 1.

sional M mode quantification is most accurate for moderate-sized effusions and less valid for small and large pericardial effusions. The apparent posterior localization of small effusions invalidates precise calculations of volumes of less than 100 ml, and implies that one dimensional studies may overestimate the size of small pericardial effusions. Likewise, the predominant posteromedial and apical localization of large pericardial effusions implies that single dimensional quantification might underestimate the size of these effusions.

Anatomic considerations in echocardiographic interpretations: It is worthwhile reviewing the anatomy of the pericardium and pericardial space to gain a better understanding of our two dimensional studies. The pericardium is a flask-like sac with its neck closed by the great vessels. The serous pericardium forms a closed sac that is reflected on itself at the exit of the great arteries and the entrance of the pulmonary veins and venae cavae. In the healthy state the two serous membranes are closely opposed to each other and contain only 10 to 15 ml of fluid.[13,14] Work by Elias and Boyd[15] has shown that the spaces called the pericardial recesses can contain a substantial amount of fluid. Anatomically, the pericardial cavity extends behind the left atrium in a recess called the oblique pericardial sinus.[13,14] This sinus is formed behind the atria by the reflection of the serous pericardium onto the venae cavae and four pulmonary veins. It is limited laterally and medially by the reflection onto the right and left pulmonary veins and superiorly by the reflection at the level of the transverse pericardial sinus. The oblique sinus is in free communication with the remainder of the pericardial cavity inferiorly and leftward. Therefore the oblique pericardial sinus covers the caudal aspect of the left atrium.

Some authors[16,17] have stated that the fluid visualized with one dimensional echocardiography posterior to the left atrium could not be pericardial because at that level the pericardium is tightly bound to the left atrium by reflections onto the pulmonary veins. Lemire et al.[18] recently demonstrated pericardial effusion posterior to the left atrium in five patients with a large effusion. Greene et al.[19] reported pericardial effusion posterior to the left atrium in a patient with a large pericardial effusion as visualized with both one dimensional and 38° mechanical sector scanning. We commonly noted a retroatrial space in our patients with a moderate or large pericardial effusion. In none of the patients with a moderate effusion did the echo-free space extend as far cephalad behind the left atrium as in the patients with a large effusion. This apparent discrepancy between M mode and two dimensional echocardiography may be a result of the lack of spatial orientation of the M mode technique and its narrow field of view. Because the oblique pericardial sinus is actually behind the inferior portion of the left atrium near the A-V groove, a one dimensional echocardiographic beam directed through the more superior aspect of the left atrium or between the right and left pulmonary veins could not visualize fluid in the oblique sinus. As the size of the pericardial effusion increased, the extension of the echo-free space behind the left atrium tended to become more cephalad and obvious. In patients with a freely oscillating heart in a large pericardial effusion, the posterior left atrial wall had anterior oscillation synchronous with the rest of the myocardium in early systole. This observation substantiates the work of Lemire et al.,[18] who suggested that the finding helped to distinguish between pleural and pericardial fluid posterior to the left atrium.

Postural redistribution of pericardial effusion: This redistribution found in our studies has clinical implications. The ease of visualizing the heart in a majority of patients in the sitting position makes this procedure a potentially useful prepericardiocentesis maneuver to exclude the possibility of fluid loculation. The apical redistribution of moderate to large pericardial effusions in the sitting position also may explain the commonly found improved yield of fluid in this position with subxyphoid pericardiocentesis. This technique may aid in the performance of pericardiocentesis.

We utilized the wide angle phased array echocardiogram in one patient in this study to visualize the pericardiocentesis needle within the pericardial sac and to assess qualitatively the amount of fluid remaining as the pericardiocentesis proceeded and to suggest positional changes as an aid to greater fluid yield. A larger series of patients is necessary to determine the exact advantages and limitations of this technique.

Findings in cardiac tamponade: Further findings of this study are related to imaging in two patients with clinically established cardiac tamponade. Short axis imaging just below the level of the mitral valve enabled us to see the right ventricular and left ventricular chambers. In both patients there was an obvious inspiratory increase in right ventricular chamber size at the expense of left ventricular chamber size. Whether this mechanism truly leads to a decreased left ventricular stroke volume and causes paradoxical pulse must await further studies using simultaneous noninvasive and hemodynamic methods. Nevertheless, reciprocal changes in ventricular diameters seen in M mode records during tamponade are confirmed here.[20,21] Such changes are not solely a result of inspiratory change in cardiac position under the single dimensional transducer.

We conclude: (1) The wide angle long and short ventricular axis sector scan images give a clear anatomic definition of the pericardial space and permit identification of pericardial effusions. (2) The distribution of the pericardial effusion within the pericardial space varies with the amount of fluid present. (3) The postural shift of the fluid apically with the upright position is primarily appreciated with moderate to large nonloculated effusions. (4) One dimensional M mode quantification appears most accurate for moderate-sized effusions and less valid for small and large pericardial effusions.

Acknowledgment

We acknowledge the excellent technical help of Marjorie Pittman and Elizabeth London and the assistance of Gretchen Selzer and Dorothy McCain in preparation of the manuscript.

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Ventricular Fibrillation During Programmed Ventricular Stimulation: Incidence and Clinical Implications

SCOTT R. SPIELMAN, MD*
ARDESHIR FARSHIDI, MD, FACC†
LEONARD N. HOROWITZ, MD, FACC‡
MARK E. JOSEPHSON, MD, FACC§

Philadelphia, Pennsylvania

Ventricular fibrillation occurred in 10 (3.3 percent) of 300 patients consecutively studied with programmed ventricular stimulation. One hundred twenty-five of these patients were studied with double ventricular extrastimuli including 68 patients with and 57 patients without documented or suspected ventricular tachycardia or fibrillation, or both. Ventricular fibrillation did not develop in response to a single ventricular extrastimulus delivered during sinus rhythm, ventricular pacing or ventricular tachycardia or in response to ventricular pacing at cycle lengths of 300 msec or greater and occurred only in response to double ventricular extrastimuli. All 10 patients who manifested ventricular fibrillation during programmed stimulation were in the group of patients with suspected or documented ventricular tachycardia or fibrillation. Ventricular fibrillation was initiated in seven patients with double ventricular extrastimuli delivered during sinus rhythm or ventricular pacing and in three patients with double ventricular extrastimuli delivered during ventricular tachycardia. Four patients had spontaneous conversion to sinus rhythm and the remainder underwent defibrillation without sequelae. Recurrent ventricular fibrillation occurred clinically in 7 of the 10 patients. This study suggests that ventricular fibrillation occurs uncommonly during programmed ventricular stimulation and only in response to double ventricular extrastimuli in patients in whom spontaneous episodes are likely to occur.

From the Electrophysiology Laboratory, Hospital of the University of Pennsylvania, Cardiovascular Section, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. This study was supported in part by grants from the American Heart Association, Southeastern Pennsylvania Chapter, Philadelphia, Pennsylvania, and the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received February 27, 1978; revised manuscript received July 11, 1978, accepted July 12, 1978.

* Recipient of a Research Fellowship Award of the Southeastern Pennsylvania Chapter of the American Heart Association, Philadelphia, Pennsylvania.

† Present address: University of Connecticut Health Center, Division of Cardiology, Farmington, Connecticut 06032.

‡ Recipient of a Career Development Investigatorship, American Heart Association, Southeastern Pennsylvania Chapter, Philadelphia, Pennsylvania.

§ Recipient of a Research Career Development Award, Grant K04 HL 00361-01 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Mark E. Josephson, MD, Electrophysiology Laboratory, 666 White Building, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

Programmed ventricular stimulation has become a widely used technique for evaluating properties of ventricular conduction, ventricular and supraventricular tachycardias and the electrophysiologic effects and therapeutic efficacy of pharmacologic agents.[1–32] Although studies have been performed with safety even in the immediate postinfarction period,[8,10,14] the incidence and clinical significance of ventricular fibrillation induced with programmed stimulation have not previously been reported. In this study we describe our observations in 10 patients with ventricular fibrillation resulting from ventricular stimulation with particular attention to (1) incidence, (2) mode of initiation, (3) termination and (4) clinical relevance.

Methods

Patients: Three hundred patients were studied with programmed ventricular stimulation including administration of single (300 patients) and double (125 patients) ventricular extrastimuli in the Cardiac Electrophysiology Laboratory between July 1973 and December 1977. The 125 patients who received double extrastimuli included 68 patients with and 57 patients without documented or suspected ventricular tachycardia or ventricular fibrillation, or both. All were in clinically stable condition and were studied more than 2 weeks after myocardial infarction. The indications for the electrophysiologic studies included the evaluation of (1) brady- or tachyarrhythmias; (2) electropharmacology of antiarrhythmic agents; (3) conduction disturbances; (4) palpitations; or (5) unexplained neurologic symptoms. In 10 of the 125 patients studied with mul-

TABLE I

Clinical Data in 10 Cases

Case no.	Age (yr) & Sex	Cardiac Diagnosis	ECG	Clinical History	Spontaneous Arrhythmias		Spontaneous Episodes of VF
					Prestudy	Poststudy	
1	73F	HCVD	LVH	Syncope	VPDs	VF	6
2	18M	No HD	WNL	Presyncope	VT	VT	0
3	53F	RHD, ASHD, VA	ASMI, RBBB	Syncope, CA	VT, VF	VT, VF	3
4	51M	ASHD/VA	IMI, IVCD	Syncope, CA	VT, VF	VT, VF	6
5	67M	No HD	WNL	Syncope, CA	VF	. . .	3
6	24M	CM	IVCD	Syncope, CA	VF	. . .	2
7	66F	ASHD	1°AVB, LAH/RBBB	Presyncope	. . .	. . .	0
8	52M	ASHD, VA	ASMI, LAH	Syncope, CA	VT, VF	VT, VF	5
9	54F	ASHD	NTMI	Syncope, CA	. . .	VT, VF	2
10	46M	No HD	WNL	Presyncope	SB	. . .	0

AF = atrial fibrillation; ASMI = anteroseptal myocardial infarction; ASHD = atherosclerotic heart disease; AVB = atrioventricular block; CA = cardiac arrest; CM = cardiomyopathy; HCVD = hypertensive cardiovascular disease; HD = heart disease; IMI = inferior myocardial infarction; IVCD = intraventricular conduction defect; LAH = left anterior hemiblock; LVH = left ventricular hypertrophy; NTMI = nontransmural myocardial infarction; RHD = rheumatic heart disease; RBBB = right bundle branch block; SB = sinus bradycardia; VA = ventricular aneurysm; VF = ventricular fibrillation; VPD = ventricular premature depolarization; VT = ventricular tachycardia; WNL = within normal limits; . . . = none documented.

tiple ventricular extrastimuli, ventricular fibrillation, as defined with standard electrocardiographic criteria,[33] was induced, and these patients form the basis of this report.

The 10 patients in whom ventricular fibrillation was induced included 6 men and 4 women ranging in age from 24 to 73 years. All underwent complete angiographic and hemodynamic study with cardiac catheterization (Table I). Three patients had no structural heart disease; in the remaining seven, coronary artery disease was the most common organic abnormality. Three of the five patients with coronary artery disease had clinical and X-ray or angiographic evidence, or both, of a left ventricular aneurysm. All 10 patients had a history of syncope or presyncope; six had had cardiac arrests. Five of the 10 had had recurrent ventricular fibrillation (two to six episodes) before the study (Table I).

The electrocardiogram during sinus rhythm was normal in three patients and revealed an old myocardial infarction in four patients. Intraventricular conduction defects were present in five patients. None demonstrated a prolonged Q-T interval or preexcitation. In all 10 patients the studies were performed to evaluate documented ventricular arrhythmias or cerebral symptoms of unclear origin. All patients had sinus rhythm at the start of the study.

Electrophysiologic studies: These studies were performed with patients in the nonsedated postabsorptive state after they had given informed consent. Multiple electrode catheters

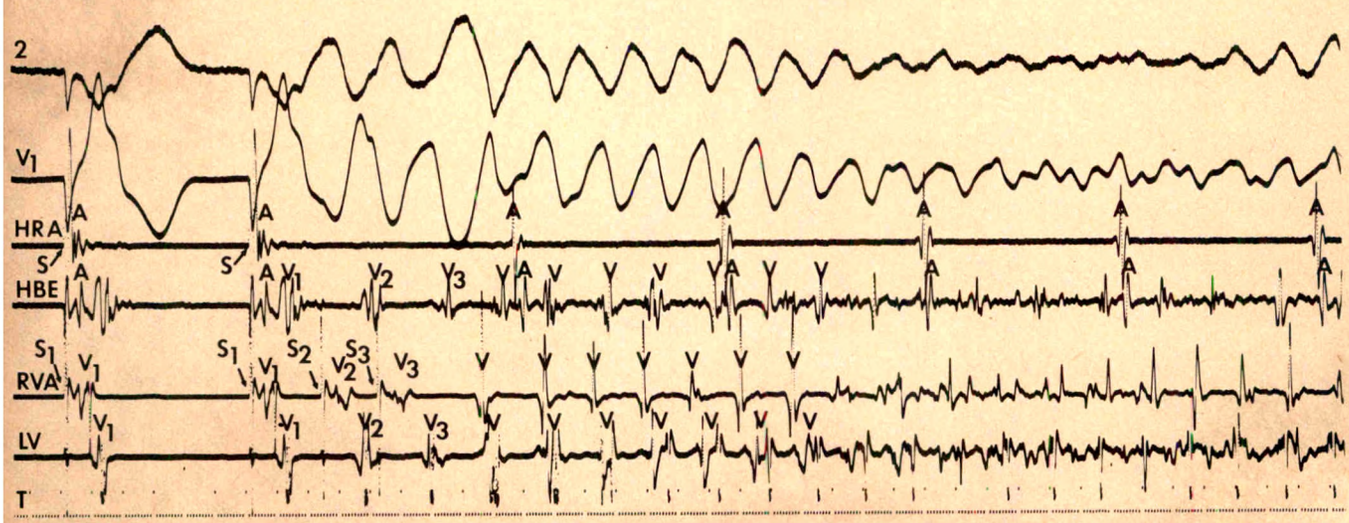


FIGURE 1. Case 8. *Initiation of ventricular fibrillation by double ventricular extrastimuli during ventricular pacing.* The panels are organized as follows: electrocardiographic leads II (2) and V_1 and electrograms from the high right atrium (HRA), His bundle area (HBE), right ventricular apex (RVA), left ventricle (LV) and time lines (10 and 100 msec) (T). During ventricular pacing at a basic cycle length (S_1-S_1) of 600 msec, two ventricular extrastimuli delivered at coupling intervals of 220 (S_1-S_2) and 180 (S_2-S_3) msec from the right ventricular apex induce ventricular fibrillation. The initiation is associated with progressive fractionation of electrograms in the His bundle area, right ventricular apex and left ventricle.

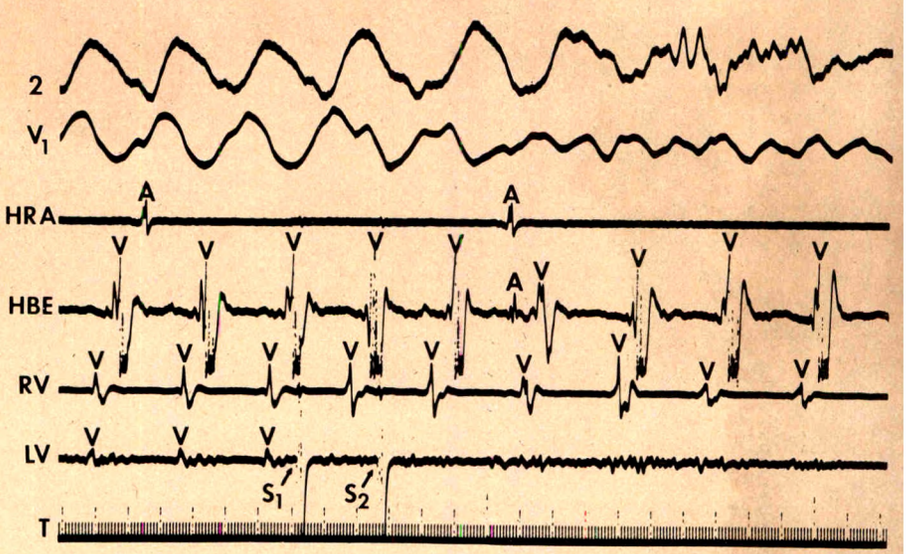


FIGURE 2. Case 3. *Initiation of ventricular fibrillation by double ventricular extrastimuli during ventricular tachycardia.* From top to bottom are electrocardiographic leads II (2) and V_1 and electrograms from the high right atrium (HRA), His bundle area (HBE), right ventricle (RV), left ventricle (LV) and time lines (10 and 100 msec) (T). Initially ventricular tachycardia is present at a cycle length of 270 msec. Double ventricular extrastimuli delivered from the mid right ventricular septum (not shown), at coupling intervals of 190 and 240 msec, initiate ventricular fibrillation. Disorganized activity is confined to the left ventricular electrogram.

were inserted either percutaneously or with a cutdown procedure and positioned in the heart under fluoroscopic control. The number of recording sites varied but usually included the high right atrium, coronary sinus, atrioventricular junction in the His bundle region, right ventricular apex and left ventricular apex. Tripolar electrode catheters were generally used for His bundle recordings; whenever recording and stimulation were required from the same site, quadripolar catheters were used. Ventricular stimulation was performed using a custom-designed programmable stimulator and an optically isolated constant current source (Bloom Associates, Ltd., Narberth, Pennsylvania).

Ventricular stimulation included: (1) Ventricular pacing at cycle lengths of 1,000 to 300 msec for at least 15 seconds. (2) Introduction of single (300 patients) and double (125 patients) ventricular extrastimuli during sinus rhythm and ventricular pacing using 1 msec square wave impulses at twice diastolic threshold (0.75 to 2 milliamperes [mA]). Single premature ventricular extrastimuli (S_2) were introduced in late diastole and the S_1-S_2 coupling interval was shortened until ventricular refractoriness was reached. When double premature stimuli (S_3) were delivered they were introduced starting at an S_1-S_2 interval 50 to 100 msec longer than the ventricular effective refractory period and at an S_2-S_3 interval equal to the S_1-S_2 interval. The S_2-S_3 interval was shortened and, when S_3 failed to evoke a V_3, the S_1-S_2 interval was decreased until S_3 could evoke a response. This method was used until both S_2 and S_3 reached refractoriness. (3) If ventricular tachycardia was initiated, premature single and double ventricular stimuli were introduced in a similar fashion in an attempt to terminate the arrhythmia. Stimulation was performed from the right ventricle in all patients. Defibrillation was required in six patients and was accomplished within 15 seconds without neurologic or cardiac sequelae.

Particular care was taken to eliminate the possibility of electrical hazards. The leakage current was measured routinely and ranged from 4 to 8 μA, a level less than that required by the electrical safety standards of the National Fire Prevention Association and the American Heart Association Committee for Electronic Equipment for Use in Human Subjects.[34]

Intracardiac electrograms were simultaneously recorded with two or three surface electrocardiographic leads and time lines on an Electronics for Medicine DR-16 recorder. The data were stored on magnetic tape (Honeywell 5600C) and subsequently retrieved on photographic paper at speeds of 100 to 200 mm/sec.

TABLE II

Electrophysiologic Data (in msec) in 10 Cases

Case no.	Interval A-H	Interval H-V	ERP-RV	Method of Induction
1	85	68	210	2 VPDs
2	85	42	240	2 VPDs
3	100	110	270	2 VPDs during VT
4	85	65	250	2 VPDs during VT
5	100	48	215	2 VPDs
6	95	85	210	2 VPDs
7	100	50	210	2 VPDs
8	85	45	245	2 VPDs during VT
9	85	55	200	2 VPDs
10	70	45	180	2 VPDs

ERP = effective refractory period; RV = right ventricle; VPD = ventricular premature depolarization; VT = ventricular tachycardia.

Results

Mode of initiation and termination: None of the 300 patients manifested ventricular fibrillation in response to single ventricular extrastimuli delivered during sinus rhythm, ventricular pacing or ventricular tachycardia. Among the 125 patients studied with double ventricular extrastimuli, ventricular fibrillation developed in 10 (8 percent). There was no difference in the stimulation techniques used in the patients who did and did not experience ventricular fibrillation; and all 10 of the patients with ventricular fibrillation were in the group of 68 patients with documented or suspected ventricular tachyarrhythmias. Ventricular fibrillation was initiated in seven patients with double premature ventricular extrastimuli introduced during sinus rhythm (two patients) or with ventricular pacing (five patients) (Fig. 1) or, in three patients, with double premature ventricular extrastimuli during ventricular tachycardia (Fig. 2) (Table II). In one patient ventric-

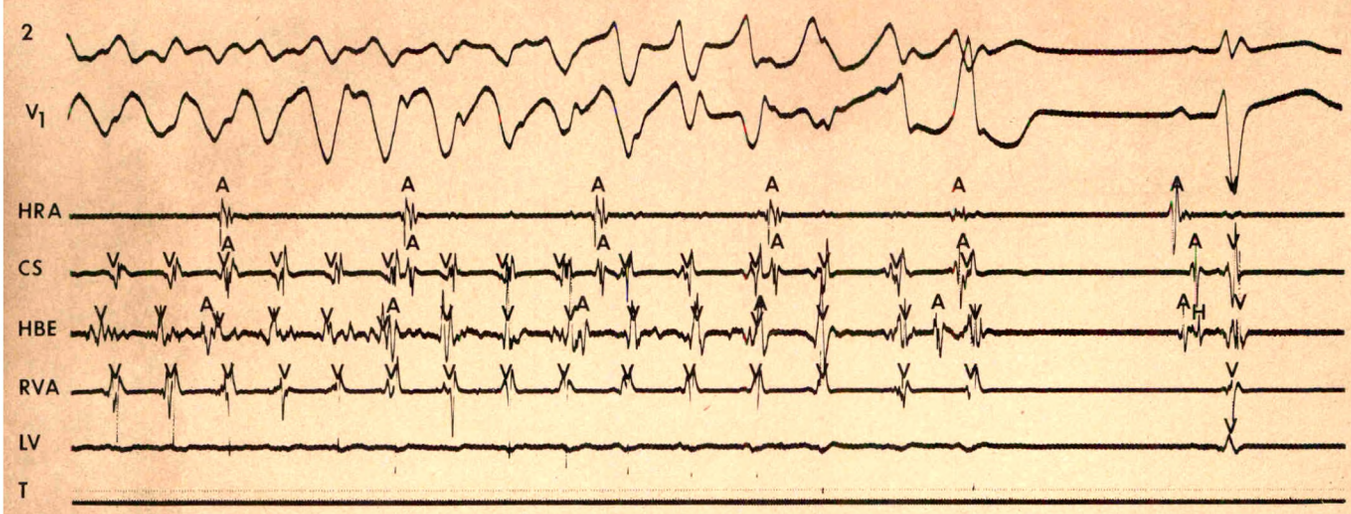


FIGURE 3. Case 2. *Spontaneous termination of ventricular fibrillation.* The tracings are organized from **top** to **bottom:** electrocardiographic leads II (2) and V_1 and electrograms from the high right atrium (HRA), coronary sinus (CS), His bundle area (HBE), right ventricular apex (RVA), left ventricle (LV) and time lines (10 and 100 msec) (T). During ventricular fibrillation disorganized ventricular activity is confined to the His bundle and left ventricular electrograms, whereas the ventricular activity in the coronary sinus and right ventricular apical electrograms remains organized. Spontaneous conversion to sinus rhythm is coincident with reorganization of the electrograms in the His bundle area and left ventricle.

ular fibrillation was induced with two ventricular extrastimuli delivered during ventricular pacing only after the intravenous administration of 1 mg of atropine sulfate.

Four patients (Cases 1, 2, 7 and 9) had spontaneous conversion to sinus rhythm. Although each patient had syncope or presyncope, only one had had a cardiac arrest clinically. In Case 2 (Fig. 3) ventricular fibrillation revealed in the surface electrocardiogram was associated with disorganized activity that was confined to two local ventricular electrograms. Spontaneous conversion occurred when organized activity reappeared in these recordings. In Case 7, three simultaneous ventricular electrograms initially showed disorganized activity (Fig. 1). Conversion to sinus rhythm was coincident with the spontaneous sequential reorganization of local electrical activity in each electrogram. Defibrillation with 100 to 400 watt-seconds was required in each of the six patients whose arrhythmia failed to convert spontaneously.

Relation of induction to spontaneous arrhythmias: Seven of the 10 patients in whom ventricular fibrillation was induced by programmed stimulation sustained it spontaneously before or after the electrophysiologic evaluation (Table I). Five patients (Cases 3 to 6 and 8) with a clinical history of syncope and cardiac arrest had documented recurrent ventricular fibrillation before the electrophysiologic study.

In five patients (Cases 1, 2, 7, 9 and 10) in whom ventricular fibrillation was initiated by programmed ventricular stimulation, ventricular fibrillation had not been documented before the electrophysiologic study. Two of these patients (Cases 1 and 9) subsequently had ventricular fibrillation spontaneously in the hospital, and both required defibrillation. In the three remaining patients ventricular fibrillation has not been noted since its laboratory initiation. One of these patients (Case 2) is arrhythmia-free on a medical regimen that was found to be successful during electrophysiologic evaluation. Another patient (Case 7) was iatrogenically thyrotoxic and is without ventricular fibrillation after reduction of thyroid medication. The final patient (Case 10), in whom ventricular fibrillation developed only after administration of atropine, has had no recurrences and is currently receiving no therapy.

Discussion

Incidence and safety: Programmed ventricular stimulation—including introduction of single and double ventricular extrastimuli and right ventricular pacing—has become a commonly used technique for evaluating ventricular tachyarrhythmias.[14–16,27,29,30,32] The overall safety of this technique has not been established, although previous reports by Wellens et al.[8,10] and Josephson et al.[14] have demonstrated that ventricular extrastimulation can be performed without morbidity or mortality in the evaluation of ventricular tachycardia, even in patients who have recently had a myocardial infarction. The present study shows that ventricular fibrillation occurred uncommonly in response to ventricular stimulation and did not develop in response to a single ventricular extrastimulus introduced during sinus rhythm, ventricular pacing or ventricular tachycardia. It occurred only in response to double ventricular extrastimuli. Among the 125 patients studied with multiple extrastimuli, ventricular fibrillation occurred only in the group of 68 patients with a history of documented or suspected ventricular tachyarrhythmias. It was not induced in any of the 57 patients who were studied with the same protocol of multiple ventricular extrastimuli but who had no history of documented or suspected ventricular tachycardia or fibrillation. In our studies no morbidity beyond that of

electrical defibrillation was associated with the induction of ventricular fibrillation.

Mechanism of initiation: The failure of single ventricular premature depolarizations to induce ventricular fibrillation during ventricular tachycardia must have an electrophysiologic explanation. Experimental data[35–38] suggest that inhomogeneity and shortened refractoriness are the prerequisities for the development of ventricular fibrillation. Although ventricular tachycardia might produce ischemia and increase dispersion of ventricular refractoriness and therefore provide the milieu for developing ventricular fibrillation, this did not occur in our group of patients. This observation suggests that ventricular refractoriness may actually have been more uniform at the rates of ventricular tachycardia observed in our patients, or simply that the increase in inhomogeneity was not sufficient to produce ventricular fibrillation. Spear et al.[39] demonstrated that ventricular premature depolarizations increase temporal dispersion of refractoriness and decrease the threshold for ventricular fibrillation. Thus in each instance the first ventricular premature depolarization shortens ventricular refractoriness and increases the inhomogeneity of recovery so that the threshold for ventricular fibrillation is lowered for the subsequent premature depolarization. In our cases, only the second ventricular premature depolarization resulted in an acceleration of responses with progressive shortening of refractoriness with the appearance of fractionated electrograms at which time ventricular fibrillation ensued.

Clinical significance: The patients who experienced ventricular fibrillation in the laboratory were being evaluated because of symptoms consistent with or documented to be related to ventricular tachyarrhythmias. Spontaneous episodes of ventricular fibrillation were documented in 7 of the 10 patients who had the arrhythmia in the laboratory. In two of these patients confirmed episodes of ventricular fibrillation had not been observed before electrophysiologic evaluation, yet spontaneous episodes resulting in cardiac arrest and requiring defibrillation occurred during the follow-up period after electrophysiologic study. This finding suggests that ventricular fibrillation induced by programmed ventricular extrastimuli primarily occurs in those patients in whom it has previously occurred or is going to occur spontaneously. In two of the three patients in whom the spontaneous occurrence of the arrhythmia has not been documented (Cases 7 and 10), the ventricular fibrillation was probably a drug-related event. Moreover, spontaneous termination noted in the laboratory occurred primarily in those patients who did not sustain a true cardiac arrest before or after study.

Several lines of evidence suggest that the ventricular fibrillation induced in our patients was not due to accidental delivery of excessive current. All of our studies were performed at twice diastolic threshold using an optically isolated current source. Chardack[40] has previously stated that pulses with an intensity of twice diastolic threshold do not induce ventricular fibrillation in a stable myocardium even when they fall during the vulnerable period. In addition, although ventricular fibrillation induced by coupled electrical stimulation has been reported in patients with, or being evaluated for, an implantable pacemaker, the minimal intensity required for the induction of ventricular fibrillation was always greater than 4 to 10 times diastolic threshold.[41–43] A theoretical basis for these observations has been demonstrated in our laboratory,[39] where we have shown that the temporal dispersion in recovery of excitability, and thus ventricular fibrillation threshold, is current-dependent and changes dramatically with increasing milliamperes.

We conclude: that (1) ventricular extrastimulation can be performed with safety in patients who are in clinically stable condition; (2) single extrastimuli delivered during sinus rhythm, ventricular pacing or ventricular tachycardia do not induce ventricular fibrillation, even in the group of patients who manifest it spontaneously or in response to multiple extrastimuli; and (3) initiation of ventricular fibrillation in the laboratory may be predictive of its spontaneous occurrence.

Acknowledgment

We gratefully acknowledge Marie Coscia for her secretarial assistance; Kathleen Sundra, Blanche Douglas, Karen Resko and Linda Branca for their technical assistance; and especially John A. Kastor, MD, Chief of the Cardiovascular Section of the Hospital of the University of Pennsylvania, for his continued support and encouragement.

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Value of a Noninvasively Induced Ventricular Extrasystole During Echocardiographic and Phonocardiographic Assessment of Patients With Idiopathic Hypertrophic Subaortic Stenosis

GERALD H. ANGOFF, MD
DANIEL WISTRAN, MD
LAURENCE J. SLOSS, MD
JOHN E. MARKIS, MD
PATRICIA C. COME, MD
PAUL M. ZOLL, MD
PETER F. COHN, MD, FACC

Boston, Massachusetts

Fifteen patients with idiopathic hypertrophic subaortic stenosis had a ventricular extrasystole induced with a new external mechanical cardiac stimulator during noninvasive evaluation of left ventricular outflow tract obstruction. Ten patients were monitored with simultaneous echocardiogram, phonocardiogram and indirect carotid pulse tracing; five were monitored with the phonocardiogram and indirect carotid pulse tracing alone. Nine of the 15 patients showed obstruction in the beat after the ventricular extrasystole, as defined by appearance of the characteristic bifid carotid pulse contour and, where recorded, an increase in systolic anterior motion of the mitral valve on echocardiography. Six patients did not show obstruction. All nine patients with obstruction had greater than 20 msec prolongation of uncorrected systolic ejection time in the postextrasystolic beat of the carotid pulse tracing. Change in the uncorrected ejection time was +0.038 ± 0.015 second (mean ± standard deviation) in these nine patients compared with −0.003 ± 0.005 second in the six not showing obstruction ($P < 0.01$). Six patients underwent cardiac catheterization: Three patients without obstruction after a noninvasively induced ventricular extrasystole had no obstruction at catheterization and three patients with obstruction after noninvasively induced ventricular premature beats demonstrated obstruction at rest or after provocative maneuvers during catheterization. These results indicate that the noninvasive induction of a ventricular extrasystole is a useful and easily performed procedure for both diagnosing and evaluating the dynamic left ventricular outflow tract obstruction of idiopathic hypertrophic subaortic stenosis.

The effect of postextrasystolic potentiation of myocardial contractility on left ventricular outflow tract obstruction is one of the well recognized physiologic characteristics of idiopathic hypertrophic subaortic stenosis. The initial report of Brockenbrough et al.[1] described a decrease in the arterial pulse pressure of the postextrasystolic beat despite an increased intraventricular pressure. This sign of idiopathic hypertrophic subaortic stenosis could be detected from simultaneous aortic and left ventricular pressure recordings, intraarterial pressure recordings or the indirect carotid pulse tracing[1,2] provided that extrasystoles either could be induced or occurred spontaneously. When present, the sign is specific[1–4,6] and has been correlated with the echocardiographic findings of obstruction.[5] White and Zimmerman[6] used the postextrasystolic beat phenomenon in a slightly different fashion, finding that the prolongation of the ejection time of the postextrasystolic beat by more than 20 msec was more sensitive than change in pulse pressure as an indicator of hypertrophic subaortic stenosis.

From the Departments of Medicine, Peter Bent Brigham Hospital, Beth Israel Hospital, and Harvard Medical School, Boston, Massachusetts. This study was supported by Grant HL-7049 from the U.S. Public Health Service, National Institutes of Health, Bethesda, Maryland. Manuscript received May 9, 1978; revised manuscript received July 11, 1978, accepted July 12, 1978.

Address for reprints: Peter F. Cohn, MD, Cardiovascular Division, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

TABLE I

Summary of Findings in 15 Cases

Case no.	Age (yr) & Sex	S/PW Ratio	MVSAM		Carotid Pulse Contour			Post-VPB		Cardiac Catheterization Findings
			Present	Septal Contact	Rest	Valsalva	Amyl Nitrite	Carotid Contour	ΔET(sec)	
A. Normal Response to Ventricular Premature Beat										
1	42M	1.5	Yes	No	NI	NI	Abnl	NI	−0.009	. . .
2*	66M	2.2	Yes	No	NI	NI	NI	NI	−0.015	No gradient with Valsalva maneuver, amyl nitrite or post-VPB
3*	60F	2.1	Equivocal	No	NI	NI	Abnl	NI	−0.004	. . .
4	16M	2.8	Yes	No	NI	NI	NI	NI	+0.006	No gradient at rest or with isoproterenol
5	60M	1.9	Yes	Yes	NI	NI	. . .	NI	0.000	No gradient at rest or post-VPB
6	49M	1.7	Yes	No	NI	Minimally abnl	. . .	NI	+0.002	. . .
Mean	. . .	. . .	. . .	. . .	. . .	. . .	. . .		0.003 ±0.005†	
B. Abnormal Response to Ventricular Premature Beat										
7	56M	1.8	Yes	No	Labile supine, abnl standing	Abnl	Abnl	Abnl	+0.066	. . .
8	30F	2.8	Equivocal	No	NI	Variably abnl	NI, abnl with Valsalva maneuver	Minimally abnl	+0.023	No gradient at rest; 9 mm Hg gradient with isoproterenol; 23 mm Hg gradient with amyl nitrite
9	72M	1.7	Yes	No	NI	Abnl	Abnl	Abnl	+0.049	. . .
10	59M	2.0	Yes	No	Labile	Abnl	Abnl	Abnl	+0.051	. . .
11*	36M	1.8	Yes	Yes	Abnl	Abnl	. . .	Abnl at rest	+0.040	70 mm Hg gradient at rest; 154 mm Hg gradient post-VPB and 14 mm Hg ↓ in arterial pulse pressure
12*	68M	1.8	Yes	No	Minimally abnl	Abnl	. . .	Abnl	+0.030	20 mm Hg gradient at rest; 80 mm Hg gradient post-VPB and 10 mm Hg ↓ in arterial pulse pressure
13	28F	2.3	Yes	No	Abnl	Abnl	. . .	Abnl	+0.021	. . .
14	56M	2.3	Yes	No	Abnl	Abnl	. . .	Abnl	+0.033	. . .
15	34M	1.6	Yes	Yes	NI	Abnl	. . .	Abnl	+0.027	. . .
Mean	. . .	. . .	. . .	. . .	. . .	. . .	. . .		+0.038 ±0.015†	

* = receiving propranolol. † = difference significant; probability (P) <0.01 (mean ± standard deviation).
↓ = decrease; Abnl = abnormal; ΔET = change in ejection time; MVSAM = mitral valve systolic anterior motion; NI = normal; PW = left ventricular posterior wall; S = ventricular septum; VPB = ventricular premature beat.

Recently, a safe noninvasive method for inducing ventricular extrasystoles was described by Zoll et al.[7] and its use in evaluating ventricular function with simultaneous echocardiography reported.[8,9] This paper illustrates the usefulness of the noninvasively induced ventricular extrasystole in the diagnosis and evaluation of idiopathic hypertrophic subaortic stenosis during either simultaneous phonocardiography and indirect carotid pulse recording or simultaneous phonocardiography, echocardiography and indirect carotid pulse recording.

Material and Methods

Patients: Fifteen patients with idiopathic hypertrophic subaortic stenosis diagnosed with noninvasive testing alone or in conjunction with cardiac catheterization had an extrasystole induced noninvasively. Criteria for inclusion in the study were the presence of sinus rhythm, lack of severe constant obstruction at rest as judged clinically and, in the case of female patients, breast tissue that could be moved away from the area of the cardiac apex. Six patients had prior or subsequent cardiac catheterization. Twelve of the 15 were studied as outpatients. Four patients were receiving propranolol at the time of study.

Noninvasive testing: *Echocardiograms* were performed with either a Smith Kline Ekoline or an Irex Cardiac Ultrasound machine using a 13 mm, 2.25 megahertz transducer. Phonocardiograms were performed with an Elema Schonander Mingograf 81, Cambridge six channel recorder (model 72112X) or simultaneously with the echocardiograms on the Smith Kline or Irex machine.

The indirect carotid pulse tracing was recorded with a funnel-shaped transducer (time constant greater than 3 seconds) in all 15 patients during the Valsalva maneuver, and in 9 patients during inhalation of amyl nitrite.

The criteria for the noninvasive diagnosis of idiopathic hypertrophic subaortic stenosis were (1) echocardiographic findings of asymmetric septal hypertrophy with a septum/posterior left ventricular wall ratio greater than 1.3[10] and systolic anterior motion of the mitral valve,[11–13] or (2) phonocardiographic findings of a systolic ejection murmur combined with a characteristic bifid carotid pulse form with quick-rising percussion wave, mid systolic dip and late tidal wave or bulge[2,3,5,14–18] at rest or with provocation (Valsalva maneuver and amyl nitrite inhalation). New or increased obstruction due to hypertrophic subaortic stenosis was believed to have developed during provocative maneuvers when there was a change in the carotid pulse to the characteristic bifid form together with an increase in the systolic ejection murmur. Although rare exceptions may exist to restrict use of these criteria in hyperkinetic states[19] (where there is still likelihood of intercavitary obstruction), the carotid pulse changes are considered virtually diagnostic.[3,5]

Induced extrasystole: During the noninvasive testing, a ventricular extrasystole was induced with chest percussion to the area of the cardiac apex using an external mechanical

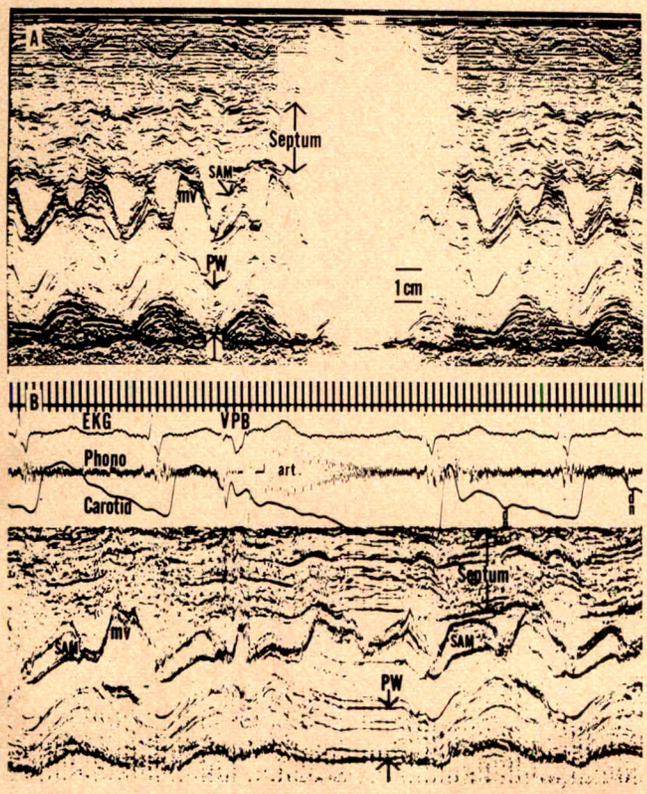


FIGURE 1. Case 7. **A**, standard echocardiogram at rest. **B**, simultaneous echocardiogram and phonocardiogram (Phono) with an induced extrasystole (VPB). Initially, there is some systolic anterior motion (SAM) of the mitral valve (mv) with a normal carotid pulse. In the postextrasystolic beat, the carotid pulse becomes abnormal and systolic anterior motion of the mitral valve becomes greatly increased in degree as well as duration with occurrence of septal contact. art. = noise artifact of percussion; dn = dicrotic notch; EKG = electrocardiogram; pw = posterior wall.

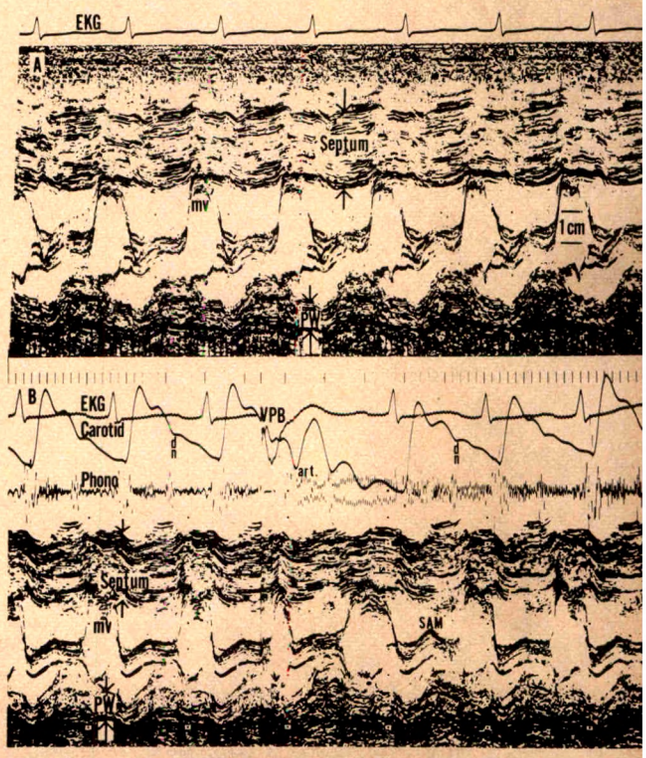


FIGURE 2. Case 8. **A**, standard echocardiogram at rest. **B**, simultaneous echocardiogram and phonocardiogram with an induced extrasystole (VPB). In the postextrasystolic beat, the carotid pulse is slightly more abnormal with a more prominent mid systolic dip, and there is systolic anterior motion (SAM) of the mitral valve (mv). Unidentified abbreviations as in Figure 1.

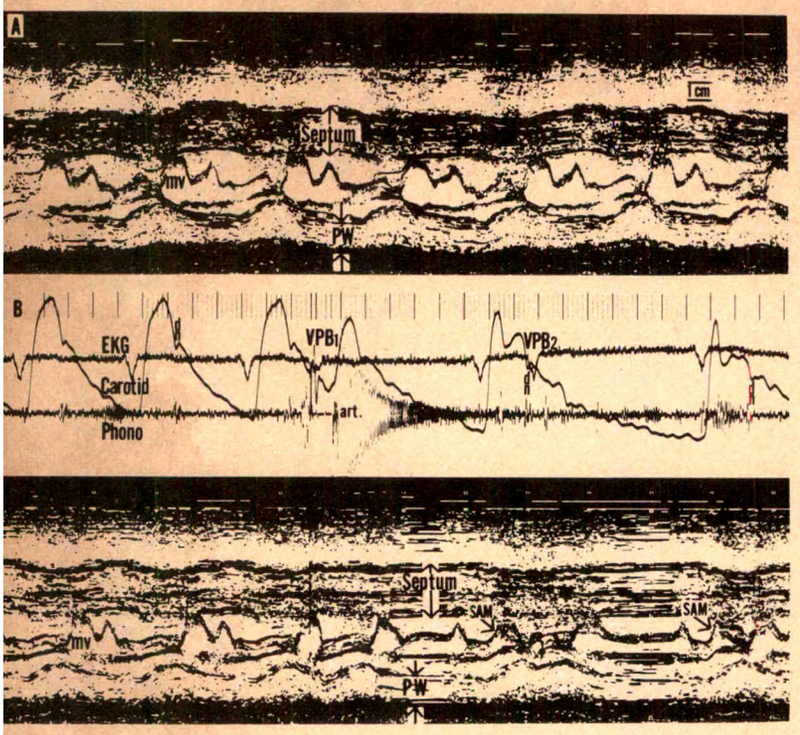


FIGURE 3. Case 9. **A**, standard echocardiogram at rest. **B**, simultaneous echocardiogram and phonocardiogram with an induced extrasystole. In the postextrasystolic beat, the carotid pulse becomes abnormal and there is marked systolic anterior motion (SAM) of the mitral valve (mv) with septal contact. Similar changes occur in the beat after a spontaneous (VPB_2) ventricular premature beat that occurs immediately after the first ventricular premature beat (VPB_2). Unidentified abbreviations as in Figure 1.

cardiac stimulator developed by Zoll et al.[7] The stimulator was a modified electrically powered stapling gun attached to a control box containing potentiators and a synchronizing switch. The stimulator was discharged manually after inscription of the T wave was observed on an oscilloscope. The energy threshold was set at approximately 1 joule.

During this maneuver, the carotid pulse and heart sounds at the left lower sternal border were recorded either alone (5 patients) or simultaneously with the echocardiogram of the base of the left ventricle at the level of the mitral valve (10 patients). Uncorrected systolic ejection time was measured in the beat before and after the extrasystole. Obstruction was believed to have developed in the beat when the carotid pulse changed to the characteristic bifid form, or when there was an accompanying increase in the degree or duration of systolic anterior motion of the mitral valve in the echocardiogram, or both.

Results

Rest: Data on the 15 patients in the study are summarized in Table I. There were 12 male and 3 female patients with an age range of 16 to 72 years. All 15 patients had asymmetric septal hypertrophy. Systolic anterior motion of the mitral valve was definitely present in 13 and was equivocally present in the other 2. Nine patients had a normal carotid pulse tracing at rest; six had a tracing that was labile in form or clearly showed the abnormal bifid form.

Provocative maneuvers: During phonocardiography and carotid pulse recording, all 15 patients underwent other obstruction-provoking maneuvers in addition to induced extrasystoles. The results and correlations with other data are listed in Table I.

Induced extrasystole: An extrasystole could be induced in most patients on either the first or the second attempt. In only one patient were several attempts unsuccessful, and this patient was not included in our series (failure to induce extrasystoles is uncommon and usually related to a thick chest wall[8]). As in previously studied patients, discomfort was minimal.

During the postextrasystolic beat, obstruction developed in 9 of the 15 patients, as demonstrated by a change in the carotid pulse and the appearance of or an increase in a systolic murmur. In these nine patients, the uncorrected ejection time was prolonged more than 20 msec compared with that in the preextrasystolic beat (Table I). The change in ejection time in the postextrasystolic beat for the six patients without obstruction was -0.003 ± 0.005 second (mean ± standard deviation); in the nine with obstruction the change was $+0.038 \pm 0.015$ second ($P < 0.01$). The simultaneous echocardiogram during the induced extrasystole in most cases showed good correlation of the mitral valve motion with phonocardiographic findings. That is, systolic anterior motion was marked in postextrasystolic beats that showed phonocardiographic evidence of obstruction (Fig. 1), or minimally present when there was minimal change in the carotid pulse (Fig. 2). In one patient, a spontaneous ventricular extrasystole occurred in proximity to the induced extrasystole, demonstrating the identical effect of spontaneous and induced extrasystoles on the echocardiogram and phonocardiogram (Fig. 3).

Cardiac catheterization: Six of the 15 patients underwent cardiac catheterization. Three of the six were taking propranolol and received it during both invasive and noninvasive testing. Three patients (Cases 2, 4 and 5) who did not show signs of obstruction after the noninvasively induced postextrasystole had no obstruction at catheterization either at rest or during provocative maneuvers. Three other patients (Cases 8, 11 and 12) who had provocable obstruction after noninvasively

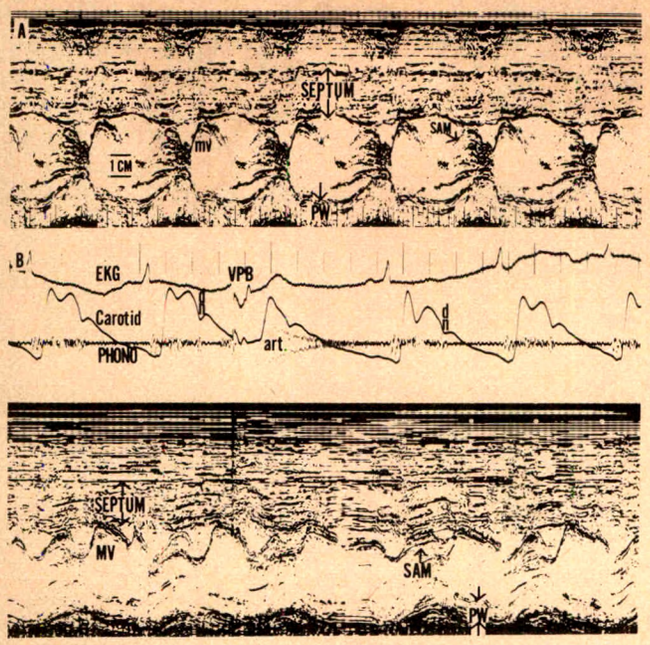


FIGURE 4. Case 11. **A**, standard echocardiogram at rest. **B**, simultaneous echocardiogram and phonocardiogram with an induced ventricular extrasystole (VPB). Initially systolic anterior motion (SAM) of the mitral valve and minimal carotid pulse abnormality are evident, and both increase in the postextrasystolic beat. Unidentified abbreviations as in Figure 1.

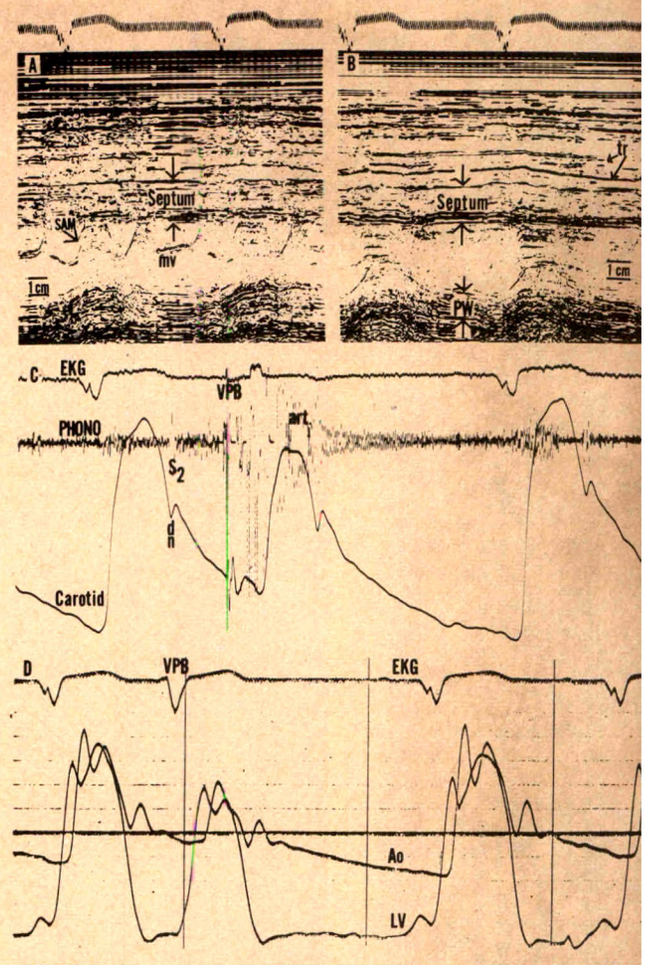


FIGURE 5. Case 5. **A**, echocardiogram at the base of the left ventricle demonstrating systolic anterior motion (SAM) of the mitral valve (mv). **B**, echocardiogram of the left ventricle demonstrating septal and posterior wall thickness. The right side of the septum is not easily determined and was conservatively chosen to avoid including right-sided trabeculations (tr) that might be considered part of the septal measurement. **C**, phonocardiogram with induced extrasystole (VBP). There is no change in the carotid pulse in the postextrasystolic beat. **D**, left ventricular (LV) and aortic (Aϕ) pressure tracings at catheterization. There is no gradient at rest or after the spontaneous extrasystole. Unidentified abbreviations as in Figure 1.

induced postextrasystolic beats had obstruction at rest or with provocation at catheterization (Table I). Of particular interest were Patients 5 and 11. Patient 11 had systolic anterior motion and carotid pulse abnormalities at rest, both of which increased in the postextrasystolic beat (Fig. 4); these findings were in agreement with catheterization data of obstruction at rest that increased with provocation. Patient 5, whose echocardiogram demonstrated systolic anterior motion of the mitral valve with prolonged septal contact (Fig. 5), had despite this finding a noninvasively induced extrasystole that correctly predicted no provocable obstruction, as shown in the pressure tracings from catheterization in the lower panel of Figure 5.

Discussion

Idiopathic hypertrophic subaortic stenosis can usually be diagnosed noninvasively from the characteristic echocardiographic[10–13] and phonocardiographic features.[2,3,5,14–18] Provocative measures such as the Valsalva maneuver and pharmacologically induced vasodilatation add further differentiating data.[16,17,20,21] However, no single criterion has by itself proved absolutely reliable. Systolic anterior motion of the mitral valve in the absence of obstruction at catheterization has been reported in congenital heart disease, right ventricular hypertrophy and coronary artery disease.[22–24] It is also becoming clear that dynamic left ventricular outflow tract obstruction can be found in states other than hypertrophic subaortic stenosis. Thus, there are reports of systolic anterior motion of the mitral valve (with obstruction) in the presence of a normal septum[25] and in the presence of concentric hypertrophy.[26] Because of these possibilities, evaluation of a patient for dynamic left ventricular outflow tract obstruction using noninvasive techniques must be done with care and with a variety of techniques, preferably in combination.

Correlation of response to mechanically induced extrasystole with other noninvasive recordings: The mechanically induced extrasystole is an easily performed safe means of delivering a potent stimulus to obstruction in patients with known or suspected idiopathic hypertrophic subaortic stenosis. The response can easily be characterized from the change in the carotid pulse tracing, and the increase in the ejection time of the postextrasystolic beat allows quantification of the effect, which can serve as a useful diagnostic tool.[6] In our small series, the carotid pulse, mitral valve motion and changes in ejection time in the postextrasystolic beat

usually correlated well with each other and were in concert with previous descriptions. The utility of the method is evident in the response of Patient 5 (Fig. 5), who was the only one in our series with discordant findings in the echocardiogram and carotid pulse tracing. In this patient the echocardiogram at rest would have incorrectly predicted the catheterization findings, whereas the carotid pulse analysis of the postextrasystolic beat was in agreement with these findings. A similar case has been reported[27] where the incorrectness of the echocardiographic prediction was evident only after catheterization.

Correlation with cardiac catheterizations: In all six patients who underwent cardiac catheterization, the postextrasystolic responses to induced ventricular extrasystoles were in excellent agreement with the catheterization findings. Three patients without obstruction after a noninvasively induced ventricular extrasystole had no obstruction at catheterization, and three patients with obstruction after noninvasively induced extrasystoles demonstrated obstruction at rest or after provocative maneuvers during catheterization. In two of the latter patients, extrasystoles occurred during the catheterization; in both patients, the arterial pulse pressure decreased. (Our series is too small to comment on whether the Brockenbrough sign is less reliable than prolongation of the ejection time in diagnosing idiopathic hypertrophic subaortic stenosis in patients with a gradient at catheterization, as suggested by White and Zimmerman.[6])

Clinical implications: On the basis of this study, we believe that the mechanically induced extrasystole is a valuable addition to the noninvasive methods available for the diagnosis and long-term evaluation of patients with idiopathic hypertrophic subaortic stenosis. The method, alone or in addition to provocation with the Valsalva maneuvers and amyl nitrite inhalation, allows easily repeated characterization of the labile hemodynamic state of the disorder. The induced extrasystole should also be useful in investigating other causes of dynamic left ventricular outflow tract obstruction.

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Effectiveness of Increasing Hours of Continuous Ambulatory Electrocardiography in Detecting Maximal Ventricular Ectopy

Continuous 48 Hour Study of Patients With Coronary Heart Disease and Normal Subjects

HAROLD L. KENNEDY, MD, MPH, FACC
VIJAY CHANDRA, MD, MPH
KARIN L. SAYTHER
DENNIS G. CARALIS, MD

Baltimore, Maryland

The effectiveness of 1, 6, 12, 24, 36 and 48 hours of continuous ambulatory electrocardiographic examination in detecting maximal ventricular ectopy was studied in 67 patients with coronary heart disease (45 with myocardial infarction, 22 with angina pectoris) and 23 normal subjects. Two consecutive 24 hour Holter recording examinations provided 48 hours of continuous examination. Ventricular ectopy was detected in 87 percent of patients and 35 percent of normal subjects. Complex forms (multifocal or repetitive patterns) were found in 62 percent and high frequency ectopy (greater than 60/hour) in 30 percent of the patients with coronary heart disease. Examination of either the initial hour of study or an hour of dynamic activity frequently failed to reveal the maximal ventricular ectopy present, particularly with regard to complex types and high frequency. Continuous 6 and 12 hour examinations were less effective than the 24 hour examination, which detected the maximal grade of ventricular ectopy in 71 to 74 percent and the maximal frequency in 58 to 83 percent of patients with coronary heart disease. Detection of maximal complex types and high frequency of ventricular ectopy was one to three times greater with a continuous 24 hour examination than with studies of shorter duration. Patient-recorded diaries showed that 50 to 80 percent of patients were engaged in mild to moderate activity during ventricular ectopy and only 9 percent indicated symptoms during the hours of maximal ventricular ectopy.

Continuous ambulatory electrocardiography is increasingly utilized to evaluate patients for a variety of clinical conditions.[1,2] This is particularly true with regard to detecting and evaluating ventricular arrhythmia in patients with coronary heart disease in whom an association and possible etiologic relation between ventricular ectopy and sudden death have been described.[3–6] Moreover, examination of ventricular ectopy for high frequency and complex types has identified subgroups of such patients at greatest risk.[3,4,6] Modern Holter recorders have extended the time of continuous electrocardiographic examination from the 6 to 12 hours obtained in the past to as long as 24 to 26 hours. With this increased time of examination has come enhanced detection of cardiac arrhythmias but also increased cost in terms of patient participation, technical analysis, data reduction and physician interpretation. The question therefore arises: How many hours of examination are really necessary?

The effectiveness of various durations of ambulatory electrocardiographic examination in detecting ventricular ectopy has only been sparsely reported.[7,8] Accordingly, we examined the effectiveness of increasing hourly durations of ambulatory electrocardiographic examination up to 48 hours in detecting maximal complex and frequent ventricular ectopy in patients with coronary heart disease and normal subjects. In addition, we reviewed the diary-recorded symptoms and activities of these subjects.

From the Department of Cardiovascular Services and Clinical Investigations, U.S. Public Health Service Hospital; the Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health; and the Department of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland. Manuscript received April 5, 1978; revised manuscript received July 18, 1978, accepted July 19, 1978.

Address for reprints: Harold L. Kennedy, MD, U.S. Public Health Service Hospital, 3100 Wyman Park Drive, Baltimore, Maryland 21211.

Materials and Methods

Subjects: Sixty-seven volunteers with ischemic heart disease and 23 normal subjects who were referred to the Department of Cardiovascular Services of the U.S. Public Health Service Hospital of Baltimore, Maryland for cardiac evaluation were recruited for study. The diagnosis of ischemic heart disease was based on a previous history of a well documented myocardial infarction or a history of typical episodes of angina pectoris and an ischemic S-T segment response on maximal treadmill exercise testing. Ischemic S-T segment response was defined as at least 1 mm of J point depression with a horizontal or downward slope for 0.08 second. Patients with recent myocardial infarction (3 months old or less) and those with unstable angina were excluded from the study. Patients were assigned to the group with myocardial infarction when they had an established diagnosis of old myocardial infarction with or without angina pectoris, and to the group with angina pectoris when they had only angina pectoris without a history or evidence of old myocardial infarction. Patients examined clinically in the Health Evaluation Clinic and found to be normal were also recruited. All subjects volunteered for two consecutive 24 hour periods of continuous examination with Holter recording; they engaged in fully ambulatory activities of clinically comparable degree during both days of the examination. Exercise testing, performed as part of each patient's cardiac evaluation after the initial 24 hour examination, was found not to influence the occurrence of ventricular arrhythmia.[9]

Holter recording procedure: All patients underwent continuous ambulatory electrocardiographic recording on 2 successive days without interruption for approximately 48 hours with use of a two channel model 425 Avionics Holter recorder (Del Mar Avionics, Irvine, California) as previously described.[10] Each patient was admonished to record carefully a chronologic diary of all physical, physiologic and emotional events to ensure comparability of activities during the 2 day examination. The electrocardiographic Holter recordings were analyzed with the model 660 Avionics Electrocardioscanner using methods previously described.[10] These methods of detecting ventricular ectopy (sensitivity) have been found to be 90 percent accurate for prevalence rates of 0 to 46 percent with a predictive positive accuracy level of 90 percent and a false positive rate of 10 percent as compared with real time printout hand counts. The qualitative accuracy of maximal grade detection was 92 percent as compared with real time printout examination. The repeatability of quantitative measurements showed no statistical differences using Student's *t* test for dependent data, and qualitative identification was found to be in agreement 89 percent of the time on three repeat examinations.

Qualitative types of ventricular ectopy were described according to Lown and Wolf[8] *as:* Grade 0, absence of ventricular ectopy; grade 1, less than two ventricular ectopic complexes/min or 30/hour; grade 2, two or more ventricular ectopic complexes/min or more than 30/hour; grade 3, multiform or multifocal ventricular ectopic complexes; grade 4A, couplets of ventricular ectopic complexes; grade 4B, three or more consecutive ventricular ectopic complexes; and grade 5, early cycle ventricular ectopic complexes with R on T phenomenon. Quantitative frequency of ventricular ectopy was reported as cumulative ventricular ectopic complexes/hour.

Data analysis: Each of the two 24 hour Holter recordings obtained per patient was examined independently for maximal grade and frequency of ventricular ectopy with the examiner unaware of the patient's clinical diagnosis, status or results of any previous Holter recording analysis. Maximal qualitative ventricular ectopy was said to occur in the earliest hour showing the highest maximal grade according to the Lown classification for that 24 hour period. The maximal frequency of ventricular ectopy was said to occur in the earliest hour showing the highest frequency range obtained according to the following arbitrarily chosen frequency ranges: 1 to 10, 11 to 60, 61 to 300, 301 to 600, or more than 600 ventricular ectopic complexes/hour. These ranges were chosen because they facilitated application of these results to prior reports based on ventricular ectopic complexes/min. A subject's two 24 hour Holter recordings were then compared to determine the earliest hour in which the maximal grade and maximal frequency of ventricular ectopy occurred during the continuous 48 hour period. The maximal frequency of ventricular ectopy of the second 24 hour Holter recording was considered greater only if it appreciably exceeded the maximal frequency of the first 24 hour recording. That is, it was considered greater only if there were a 200 percent increase over a first Holter recording showing 1 to 10 complexes/hour, a 100 percent increase over a recording showing 11 to 60 complexes/hour or a 50 percent increase over a recording showing 61 or more complexes/hour.

To determine the value of only 1 hour of Holter recording, the first 24 hour recording was examined with regard to the initial 1 hour of examination and also an hour of dynamic activity (for example, walking or working), as indicated in the patient's diary. Dynamic activity was judged verified if during the reported activity there was a trend increase in heart rate of 25 percent over the preactivity heart rate.

Similarly, various durations of 6, 12, 24, 36 and 48 hours were examined independently for their effectiveness in detecting maximal ventricular ectopy. Additionally, 24 hours of waking activity only (obtained in the initial 12 hours of each Holter recording) was examined for ventricular ectopy.

Once the hour of maximal grade and maximal frequency was identified for each patient, the diaries were reviewed for identification of symptoms and activities recorded during that hour. Arbitrarily, activity was classified as sleeping, mild activity (sitting, eating, reading, watching television), moderate activity (office work, light housework, driving) and strenuous activity (vigorous exercise, lawn work, sexual intercourse, heavy lifting).

Results

Clinical Characteristics

Two consecutive 24 hour Holter recordings were obtained in 67 patients with coronary heart disease and 23 normal subjects. The patient group consisted of 45 patients with old myocardial infarction (mean age 58 years) and 22 patients with angina pectoris (mean age 56 years). Sixty percent (27 of 45) of the patients with myocardial infarction had angina pectoris. Only seven patients were receiving cardiac medications at the time of examination; five of these were taking both digitalis and an antiarrhythmic drug. Continuous ambulatory electrocardiography detected the presence of *any* ventricular ectopy in 87 percent (39 of 45) of the patients with myocardial infarction, 86 percent (19 of 22) of those with angina pectoris and 35 percent (8 of 23) of normal subjects.

The distribution of the maximal qualitative grades of ventricular ectopy detected in the patient groups is shown in Figure 1. Of the 24 patients whose records showed no ventricular ectopy (grade 0) during the 48 hours of examination, the majority were normal

subjects. Of the 66 subjects exhibiting ventricular ectopy, 62 percent (41 of 66) were found to have complex forms of multifocal, repetitive patterns or the R on T phenomenon. Figure 2 shows the distribution of the maximal frequency of ventricular ectopic complexes/hour detected during the 48 hours of continuous ambulatory electrocardiography in the 66 patients found to have ventricular ectopy. Four patients with myocardial infarction found to have ventricular ectopy were excluded from the latter analysis because technical artifact prevented accurate quantitation of all 48 hours of ambulatory electrocardiographic data. Thirty percent (16 of 54) of patients with coronary heart disease were found to have maximal ventricular ectopy of more than 60 complexes/hour. This was considered high frequency, whereas the maximal frequency of all normal subjects ranged between 1 and 10 complexes/hour.

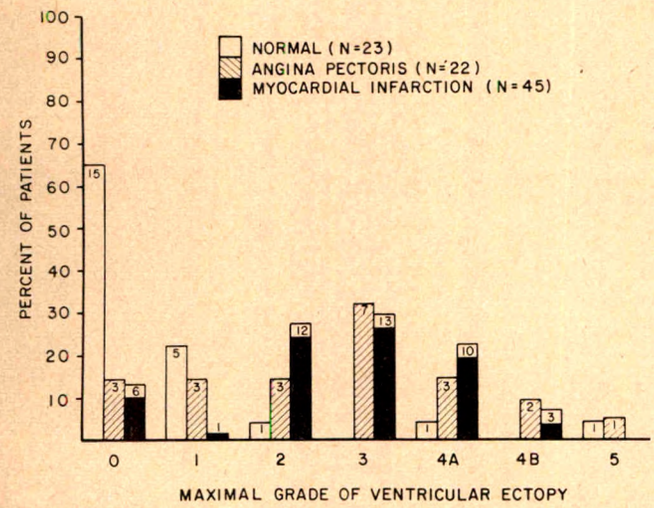


FIGURE 1. The distribution of maximal grades of ventricular ectopy with continuous 48 hour ambulatory electrocardiography in normal subjects and patients with angina pectoris or myocardial infarction. Numbers on the bars indicate number of patients in the respective groups. N = number of patients.

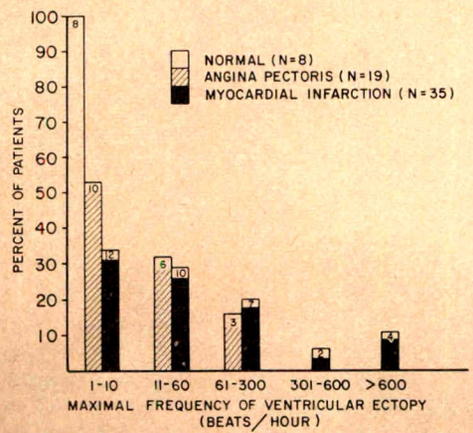


FIGURE 2. The distribution of maximal frequency of ventricular ectopy detected with continuous 48 hour ambulatory electrocardiography in normal subjects and patients with angina pectoris or myocardial infarction.

Detection of Ventricular Ectopy

The cumulative percent of patients in whom maximal ventricular ectopy was detected with increasing hours of ambulatory electrocardiography is shown in Figure 3. The rate of detection at maximal frequency of ventricular ectopy was linear, a constant incremental discovery rate occurring with time in all patient groups. In contrast, the rate of detection of the maximal grade of ventricular ectopy showed a period of early or increased discovery in the initial hours of examination, particularly in patients with myocardial infarction.

Short-term examination: *One hour examination* (either the initial hour of study or an hour of dynamic activity from the first 24 hour examination) was considerably less effective than longer examination periods in detecting maximal grade or maximal frequency of ventricular ectopy in all patient groups (Fig. 3). One hour of dynamic activity appeared superior to the initial hour of examination and, surprisingly, disclosed the maximal grade and frequency of ventricular ectopy in approximately 50 percent of patients with myocardial infarction (Table I). But in patients with angina pectoris and normal subjects, neither 1 hour study was a good detector of maximal grade or frequency of ventricular ectopy. Among all patients with coronary heart disease, the initial hour of recording detected only 26 percent of those with complex types of ectopy (ventricular couplets or runs or R on T phenomenon) and only 13 percent of those with a high frequency of ectopy (more than 60 complexes/hour). The respective figures for the 1 hour recording of dynamic activity were 21 and 19 percent.

The 6 hour examination disclosed the maximal grade of ventricular ectopy in 63 percent and the maximal frequency in 29 percent of patients with myocardial

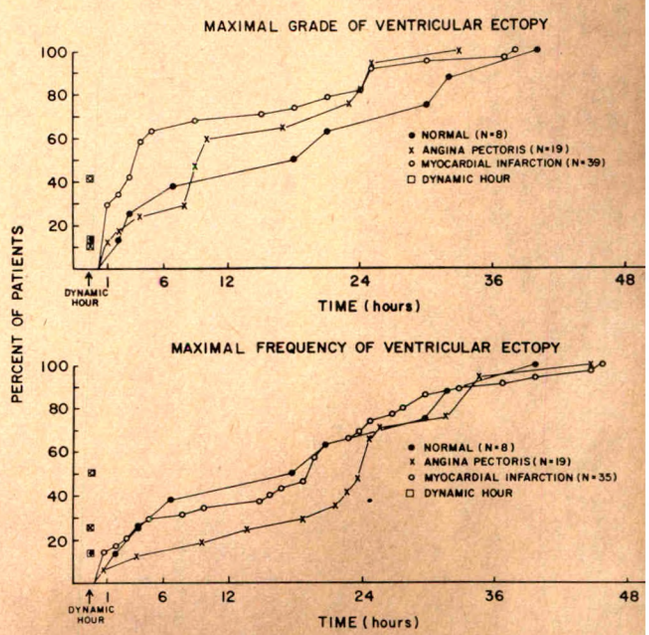


FIGURE 3. The cumulative percent of patients in whom the maximal grade of ventricular ectopy **(top)** and maximal frequency of ventricular ectopy **(bottom)** were detected with increasing durations of continuous ambulatory electrocardiography during 48 hours of examination.

TABLE I

Detection of Maximal Grade and Maximal Frequency of Ventricular Ectopy With 1 Hour Ambulatory Electrocardiography in Patients with Coronary Heart Disease and Normal Subjects

Clinical Diagnosis	Maximal Grade			Maximal Frequency		
	Total Patients	Initial Hour	Dynamic Hour	Total Patients	Initial Hour	Dynamic Hour
Myocardial infarction	39	13(33)	18(46)	35	3(9)	18(51)
Angina pectoris	19	2(11)	2(11)	19	2(11)	5(26)
Normal	8	0(0)	1(13)	8	0(0)	1(14)

Figures in parentheses indicate percent of patients.

infarction (Tables II and III). However, it detected maximal ventricular ectopy in only 25 percent of patients with angina pectoris and normal subjects. When analyzed with regard to detection of only complex forms or high frequency of ventricular ectopy, the 6 hour examination disclosed 33 to 50 percent of such arrhythmia in patients with coronary heart disease. The 1 hour examination of dynamic activity and the initial 6 hour examination showed surprising similarity in overall effectiveness in detecting maximal ventricular ectopy in patients with myocardial infarction (Fig. 3).

Long-term examination: Hourly increases in the duration of examination resulted in increasing detection of maximal ventricular ectopy (Fig. 3). The maximal grade of ventricular ectopy was detected in 71 to 74 percent of patients with coronary heart disease by 24 hours, and in 95 to 100 percent of patients by 36 hours of examination (Table II). Noteworthy, 24 hours of waking activity only (that is, the initial 12 hour period of each of the two 24 hour Holter recordings) revealed the maximal grade of ventricular ectopy in 90 percent of patients with coronary heart disease and 75 percent of normal subjects. When the data were examined with reference to detecting only complex grades of ventricular ectopy, the 24 hour continuous record was superior to the record of 24 hours of waking activity only.

Detection of maximal frequency of ventricular ectopy was progressively enhanced by longer periods of examination (Fig. 3). Although the maximal frequency was detected in only 37 to 57 percent of patients with coronary heart disease with a 12 hour examination, it was detected in 58 to 83 percent with 24 hours of examination (Table III). Unlike the detection of maximal grade, detection of the maximal frequency of ventricular ectopy in patients with coronary heart disease and normal subjects was not appreciably better with a 24 hour examination of waking activity only than with a continuous 24 hour examination. Moreover, detection of only high frequency ventricular ectopy, present only in patients with coronary heart disease, was quite effective with the continuous 24 hour examination, which disclosed 67 to 85 percent of such arrhythmia. This finding suggests that in some patients with coronary heart disease the maximal frequency of ventricular ectopy occurs during sleep.

Symptoms and Activities During Maximal Ventricular Ectopy

More than half of all patients with coronary heart disease (24 with myocardial infarction, 15 with angina pectoris) and 3 normal subjects had diary-recorded symptoms during the 48 hour examination. These symptoms consisted of chest pain or discomfort (87 percent), shortness of breath (21 percent), palpitations (15 percent) and dizziness or lightheadedness (13 percent) in the patients with coronary heart disease. Only three patients with myocardial infarction and two with angina pectoris recorded a symptom during the hour of maximal grade or frequency of ventricular ectopy; these were chest pain in four patients (all had concurrent ischemic S-T segment depression) and dyspnea in one patient. Fifty-five percent (23 of 42) of all patients with a diary-recorded complaint had no ventricular ectopy during the hour of their complaint.

Review of activities showed that maximal ventricular ectopy most commonly occurred during mild to moderate activity (Table IV). Less than one quarter of the patients with coronary heart disease were engaged in strenuous activities and 8 to 26 percent were sleeping during the hour of maximal ventricular ectopy.

Discussion

Clinical value of increased duration of Holter recording: The effectiveness of continuous ambulatory electrocardiography in detecting ventricular ectopy in patients with coronary heart disease and normal subjects, as compared with other methods, has been established.[11,12] However, limited information exists with regard to the relative effectiveness of various durations of such recordings.[7,8] This study examined and compared the effectiveness of the more commonly used hourly durations of ambulatory electrocardiography in detecting maximal ventricular ectopy, and the results support the previous speculation[7,8] that increasing the time of examination reveals more severe types and greater frequency of ventricular ectopy. This was also true for ventricular ectopy of the more ominous complex grades and greater frequency, which one might have expected to be rapidly detected with a relatively few hours of examination.

TABLE II

Detection of All Maximal Grades and Complex Grades of Ventricular Ectopy With Increasing Durations of Continuous Ambulatory Electrocardiography

Clinical Diagnosis	Total Patients	1st Holter Recording 6 Hours*	12 Hours*	24 Hours*	2nd Holter Recording 36 Hours*	48 Hours*	Waking Activity Only (24 hours*)
			All Maximal Grades				
Myocardial infarction	39	24(63)	26(67)	28(71)	37(95)	39(100)	35(90)
Angina pectoris	19	4(24)	12(63)	14(74)	19(100)	19(100)	17(90)
Normal	8	2(25)	4(50)	5(63)	7(88)	8(100)	6(75)
			Complex Grades†				
Myocardial infarction	13	4(33)	5(42)	10(77)	12(92)	13(100)	9(69)
Angina pectoris	6	3(50)	4(67)	5(83)	6(100)	6(100)	3(50)
Normal	2	1(50)	1(50)	1(50)	2(100)	2(100)	2(100)

Figures in parentheses indicate percent of patients.
* Hours = total hours of recording.
† Complex grades = ventricular couplets and tachycardia and R on T phenomenon.

TABLE III

Detection of All Maximal Frequencies and High Frequencies of Ventricular Ectopy With Increasing Durations of Continuous Ambulatory Electrocardiography

Clinical Diagnosis	Total Patients	1st Holter Recording 6 Hours*	12 Hours*	24 Hours*	2nd Holter Recording 36 Hours*	48 Hours*	Waking Activity Only (24 hours*)
			All Maximal Frequency Rates				
Myocardial infarction	35	10(29)	20(57)	29(83)	35(100)	35(100)	25(74)
Angina pectoris	19	2(11)	7(37)	11(58)	18(95)	19(100)	14(75)
Normal	8	8(25)	4(50)	7(88)	8(100)	8(100)	5(63)
			High Frequency Rates†				
Myocardial infarction	13	6(46)	8(62)	11(85)	13(100)		10(77)
Angina pectoris	3	1(33)	1(33)	2(67)	3(100)		2(67)
Normal	0						

Figures in parentheses indicate percent of patients.
* Hours = total hours of recording.
† High frequency rate = greater than 60 beats/hour.

TABLE IV

Activities of Patients and Normal Subjects During Ventricular Ectopy

Clinical Diagnosis	Patients (no.)	Activities During Hour of Maximal Ventricular Ectopy Sleep	Mild	Moderate	Strenuous
Myocardial infarction					
Grade	39	3(8)	17(44)	12(31)	7(18)
Frequency	35	3(9)	22(63)	9(26)	1(3)
Angina pectoris					
Grade	19	2(11)	8(42)	5(26)	4(21)
Frequency	19	5(26)	6(32)	4(21)	4(21)
Normal					
Grade	8	2(25)	2(25)	2(25)	2(25)
Frequency	8	3(37)	1(13)	3(37)	1(13)

Figures in parentheses indicate percent of patients.

Previous ambulatory electrocardiographic studies[3,4,13] have established an association between both complex grades and high frequency rates of ventricular ectopy and an increased risk of death and sudden death in patients with coronary heart disease and apparently healthy persons with cardiovascular risk factors. Thus, the identification of those arrhythmic forms seems especially pertinent in such patients. Our data show that ambulatory electrocardiography recordings of less than 24 hours' duration underdetect the maximal ventricular ectopy of patients with coronary heart disease, particularly with regard to defining complex grades or high frequency rates. This supports the previous data of Lopes et al.,[7] who recommended a 24 hour continuous ambulatory electrocardiogram to characterize an individual patient's arrhythmia, and confirms their observation that in approximately 25 percent of patients with coronary heart disease maximal ventricular ectopy occurs during sleep.

Although Lown and Wolf[8] reported that short-term continuous electrocardiographic studies of an initial 1 hour disclosed ventricular ectopy in 49 percent of patients with myocardial infarction, less than 25 percent of the patients who manifested complex ventricular ectopy were so detected by such brief examinations. Our data are consistent with those observations and furthermore show that 1 hour ambulatory electrocardiography examination of dynamic activity is superior to that of an initial hour of study in disclosing maximal ventricular ectopy. Recent population studies[6] have employed 1 hour examination to detect and characterize ventricular ectopy and establish associations with early mortality and sudden coronary death. However, clinicians should appreciate that such an initial examination in an individual patient with coronary heart disease would measurably underdetect an appreciable proportion of persons who manifest complex grades of frequent ventricular ectopy at times other than the initial hour of examination. That complex grades or frequent ventricular ectopy detected after several hours of recording has equal prognostic importance is widely known from previous ambulatory electrocardiographic studies.[3,4,13] These factors should be borne in mind when such limited examinations are advocated as a cost-effective measure.[14]

Correlation of maximal ventricular ectopy with symptoms: This study confirms, as indicated by patient diaries, the general clinical finding that most patients are asymptomatic during their hours of maximal ventricular ectopy. Only 9 percent of patients with coronary heart disease with ventricular ectopy recorded a symptom during the hours of maximal ventricular ectopy, whereas 55 percent recorded complaints during hours of no ventricular ectopy. Hours of maximal ventricular ectopy occurred most commonly during mild to moderate everyday activities and in only a quarter or less of patients during strenuous activity. As indicated by one peer reviewer of this study, in spite of the limitations of diary records, these observations suggest the limited anticipated benefit of patient-activated sample or event recorders in detecting maximal ventricular ectopy.

Implications: Our findings support the use of initial ambulatory electrocardiographic examination of patients with coronary heart disease using continuous 24 hour recording to detect maximal ventricular ectopy as previously advocated,[7] and suggest that a continuous 36 hour recording may be more appropriate for some patients at high risk of serious ventricular arrhythmias, such as survivors of primary ventricular fibrillation.[15] Follow-up evaluations might be expected to be adequate with shorter hours of recording and appropriate extension of recording for persons who demonstrate maximal ventricular ectopy during sleep.

Acknowledgment

We gratefully acknowledge the technical assistance of Madeleine E. Boruta, the secretarial assistance of Ellen L. Chenoweth, and the manuscript review of Janet E. Pescarmona.

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Effects of Digitalis on Ventricular Myocardial and His-Purkinje Refractoriness and Reentry in Man

JOSEPH ANTHONY C. GOMES, MD, FACC
MALKIAT S. DHATT, MD, FACC
MASOOD AKHTAR, MD, FACC
CLARITA R. CARAMBAS, MD
DAVID S. RUBENSON, MD
ANTHONY N. DAMATO, MD

Staten Island, New York

The effects of digitalis on retrograde conduction and refractoriness of the His-Purkinje system, ventricular myocardium and reentry within the His-Purkinje system were studied in 17 patients using the ventricular extrastimulus (V_2) technique. Studies were performed, before and 30 minutes after intravenous administration of ouabain, 0.01 mg/kg. After treatment with ouabain, there was a significant decrease in the functional refractory period (266 ± 19 to 254 ± 18 msec, $P < 0.001$), relative refractory period (253 ± 17 to 240 ± 16 msec, $P < 0.001$) and effective refractory period (242 ± 23 to 231 ± 24 msec, $P < 0.005$) of the ventricular muscle. In contrast, there was no significant change in retrograde His-Purkinje conduction and refractoriness. The phenomenon of reentry within the His-Purkinje system characterized by the reentrant beat (V_3) at critical retrograde conduction delays in the His-Purkinje system (V_2-H_2) within a narrow range of V_1-V_2 intervals was seen in 10 of 17 patients. Ouabain increased and shifted to the left the zone of reentry within the His-Purkinje system in 7 of 10 patients (36 ± 23 to 55 ± 23 msec, $P < 0.001$) and decreased it by 10 to 30 msec in the remaining 3 patients. The critical V_2-H_2 (186 ± 29 to 193 ± 27 msec, difference not significant [NS]) and V_1-V_2 (299 ± 30 to 294 ± 36 msec, NS) intervals for reentry did not significantly change after ouabain. However, the minimal V_1-V_2 intervals (266 ± 26 to 253 ± 25 msec, $P < 0.025$) decreased significantly, whereas the maximal V_2-H_2 intervals (266 ± 40 to 239 ± 37 msec, $P < 0.01$) increased significantly.

Thus, in the intact human heart, digitalis (1) significantly decreased all measures of ventricular myocardial refractoriness, (2) had no significant effect on retrograde conduction and refractoriness of the His-Purkinje system, and (3) widened the zone of reentry within the His-Purkinje system due to shortening of the functional refractory period of the ventricular muscle with attainment of longer V_2-H_2 delays.

The effects of digitalis on the atrioventricular node[1–5] (delay in conduction and increase in refractoriness) often preclude determination of the drug's effect on the His-Purkinje system during anterograde conduction studies. In this study we assessed the effects of digitalis on retrograde conduction and refractoriness within the His-Purkinje system and the ventricular myocardium in 17 patients using the ventricular extrastimulus technique. These studies also permitted evaluation of the drug's effect on a form of reentry within the His-Purkinje system involving a macrocircuit comprising ventricular muscle, the left and right bundle branches and the bundle of His.[6–8]

Material and Methods

Patients: Right heart catheterization was performed in 17 patients in the postabsorptive nonsedated state. The experimental nature of the procedure was explained to all patients and signed consent obtained. Ten patients underwent diagnostic electrophysiologic studies because of a history of palpitations and

From the Cardiology Department, U.S. Public Health Service Hospital, Staten Island, New York. This work was supported in part by Project HL 12536-07 of the Bureau of Medical Services, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received June 26, 1978, accepted July 19, 1978.

Address for reprints: Joseph Anthony C. Gomes, MD, Cardiology Department U.S. Public Health Service Hospital, Staten Island, New York 10304.

four patients because of sinus bradycardia and dizziness. The remaining three patients were volunteers. Pertinent clinical data on the 17 patients are provided in Table I. No patient had acute myocardial ischemia or infarction, metabolic or electrolyte abnormalities, Wolff-Parkinson-White syndrome or ventricular-atrial accessory pathways. No patient had been taking cardioactive medications for at least 7 days before the study. The QRS complex was normal in 16 patients and had a right bundle branch block pattern in 1 patient.

Procedure and measurements: Under local anesthesia and with use of the percutaneous Seldinger technique three quadripolar catheters were introduced and fluoroscopically positioned at (1) the lateral wall of the right atrium, (2) right ventricular apex, and (3) the region of the tricuspid valve to record His bundle activity.[9] The proximal pair of electrodes of the atrial and ventricular catheters were used to record electrograms and the distal pair to stimulate the atrium and ventricle electrically.

One or more standard electrocardiographic leads and precordial lead V_1, intracardiac electrograms (recorded at 40 to 500 hertz) and time lines (generated at 10, 100 and 1,000 msec) were displayed on a multichannel Electronics for Medicine oscilloscope and recorded on magnetic tape. The records were subsequently replayed and recorded on photographic paper at a paper speed of 150 mm/sec. Paced atrial and ventricular cycle lengths were scanned at 10 msec intervals utilizing extrastimuli after every eighth paced beat, using a programmed digital stimulator capable of delivering rectangular impulses 1.5 msec in duration at twice diastolic threshold. After control anterograde and retrograde studies were performed, ouabain 0.01 mg/kg body weight was administered intravenously to all 17 patients and studies were repeated 30 minutes after drug administration. Statistical analysis was performed using the Student's *t* test for paired and unpaired data.

TABLE I

Clinical Features of 17 Patients

Case no.	Age (yr) & Sex	Clinical Diagnosis	Resting ECG
1	39 M	No known heart disease	Normal
2	25 M	No known heart disease	Normal
3	62 M	No known heart disease	Normal
4	37 M	No known heart disease	Normal
5	61 M	No known heart disease	Normal
6	69 M	ASHD	APCs
7	68 M	No known heart disease	Sinus bradycardia
8	66 M	No known heart disease	Sinus bradycardia
9	60 M	ASHD	Normal
10	32 F	No known heart disease	Normal
11	48 M	No known heart disease	Normal
12	42 M	No known heart disease	Normal
13	30 F	No known heart disease	Normal
14	64 M	ASHD	Sinus bradycardia, old DMI
15	76 M	ASHD	Sinus bradycardia, RBBB
16	62 M	ASHD	Old DMI
17	63 M	ASHD	Old DMI

APCs = atrial premature complexes; ASHD = atherosclerotic heart disease; DMI = diaphragmatic wall infarction; ECG = electrocardiogram; RBBB = right bundle branch block.

Definition of Terms

S_1, V_1, H_1 and A_1 represent the stimulus artifact, ventricular electrogram, His bundle electrogram and atrial electrogram, respectively, of the basic drive.

S_2, V_2, H_2 and A_2 represent the stimulus artifact, ventricular electrogram, His bundle electrogram and atrial electrogram, respectively, of the premature depolarization (extrastimulus).

Anterograde refractory periods and conduction intervals are defined as previously described.[10]

Retrograde His-Purkinje refractory periods: *The functional refractory period of the His-Purkinje system* is the shortest V_1-H_2 interval in response to any range of V_1-V_2 intervals.[11]

The effective refractory period of the His-Purkinje system is the longest V_1-V_2 interval wherein V_2 blocks below the bundle of His. This value can be determined only if H_2 is clearly identified before retrograde block.

TABLE II

Retrograde His-Purkinje Data (in msec) in 17 Patients

Case no.	CL	His-Purkinje System: Retrograde FRP C	Retrograde FRP D	Retrograde ERP C	Retrograde ERP D	V_1-V_2 at Which H_2 Emerged From V_2: C	D	V_2-H_2 (range): C	D
1	800	530	515	NA	NA	350	350	145–250	140–300
2	650	455	490	310	310	370	370	135–230	135–245
3	700	460	460	NA	300	350	350	120–250*	110–NA*
4	500	415	420	NA	NA	300	310	120–200	120–210
5	540	390	405	NA	NA	300	300	120–150	115–170
6	550	440	445	NA	320	330	340	115–205	108–220
7	900	530	530	NA	NA	400	400	140–250	140–250
8	650	520	520	NA	NA	380	380	170–275	180–290
9	800	510	510	NA	NA	370	370	170–250	160–250
10	600	430	425	310	320	320	340	120–170	90–190
11	600	420	440	NA	NA	300	300	130–170	145–200
12	700	470	465	NA	NA	330	330	140–195	135–190
13	600	470	470	NA	330	330	340	145–205	145–210
14	700	500	505	NA	330	360	350	170–230	160–250
15	500	450	440	NA	290	310	330	140–210*	125–NA
16	700	500	510	330	320	380	380	145–250	140–250
17	550	480	480	260	260	350	320	145–245	160–260
Mean ± SD		469 ± 42	472 ± 39	302 ± 30	306 ± 23	343 ± 31	345 ± 29	140 ± 18 to 218 ± 37	142 ± 26 to 232 ± 38
P value			NS		NS		NS		NS–<0.005

* Not included in the mean values.

C = control; CL = cycle length; D = digitalis (ouabain); ERP = effective refractory period; FRP = functional refractory period; HPS = His-Purkinje system; NA = not attained; NS = not significant; *P* = probability (difference from control value); SD = standard deviation.

Ventricular myocardial refractory periods: *The functional refractory period of the ventricular muscle* is the shortest V_1-V_2 interval in response to any range of S_1-S_2 intervals.

The relative refractory period of the ventricular muscle is the longest S_1-S_2 interval at which S_2 is conducted to the ventricle with latency between the premature stimulus artifact (S_2) and the local ventricular electrogram (V_2).

The effective refractory period of the ventricular muscle is the longest S_1-S_2 interval that does not evoke a ventricular response.

Retrograde conduction intervals and determinants of reentry within the His-Purkinje system: *The V_2-H_2 interval* is the interval from the stimulus artifact or the local ventricular electrogram (V_2) (in the presence of latency) to the onset of the retrograde His bundle deflection (H_2). It is taken as a measure of retrograde His-Purkinje conduction during premature ventricular stimulation. The minimal and maximal V_2-H_2 intervals refer to the shortest and longest V_2-H_2 intervals, respectively.

The V_2-H_2 gap zone refers to the range of V_1-V_2 intervals over which V_2 impulse blocks in retrograde manner in both bundle branches (that is, V_2 is not followed by H_2).[8]

The critical V_1-V_2 interval is the longest V_1-V_2 interval manifesting reentry.

The critical V_2-H_2 interval is the shortest V_2-H_2 interval required for reentry.

The maximal V_2-H_2 interval for reentry is the longest V_2-H_2 interval in response to any V_1-V_2 interval for reentry.

The zone of reentry is the range of V_1-V_2 coupling intervals over which reentry is manifest.

Results

Anterograde Conduction and Refractoriness

Ouabain significantly slowed the sinus rate (R-R interval = 828 ± 212 to 943 ± 281 msec, probability [P] < 0.025) and increased the A-H interval (86 ± 15 to 93 ± 17 msec, $P < 0.005$), atrial cycle length for atrioventricular (A-V) nodal Wenckebach block (384 ± 74 to 416 ± 91 msec, $P < 0.005$) and the functional refractory period of the A-V node (414 ± 52 to 438 ± 58 msec, $P < 0.025$). The effective refractory period of the A-V node increased (by 10 to 40 msec) in three patients in whom it could be determined during the control study. In another six patients the effective refractory period of the A-V node was attained after administration of ouabain; during the control study, it was limited by atrial refractoriness. The effective refractory period of the atrium decreased insignificantly after ouabain (251 ± 32 to 243 ± 36 msec, difference not significant [NS]). During anterograde studies, His-Purkinje system refractoriness could not be determined in any of the patients either before or after drug administration.

Retrograde Conduction and Refractoriness

Retrograde His-Purkinje conduction: During progressive premature stimulation of the ventricles, a point was reached (that is, the V_1-V_2 interval) where the retrograde His bundle electrogram emerged from the ventricular electrogram. Thereafter an inverse relation existed between V_1-V_2 and V_2-H_2 intervals. The V_2-H_2 intervals, which were used as a measure of retrograde His-Purkinje conduction time, ranged from 120 to 275 msec during the control study. The average minimal V_2-H_2 interval (140 ± 18 to 142 ± 26 msec, NS) and the average V_1-V_2 intervals at which H_2 emerged from the V_2 electrogram (343 ± 31 to 345 ± 29 msec, NS) did not significantly change after ouabain (Table II). However, the average maximal V_2-H_2 intervals were significantly longer (218 ± 37 to 232 ± 38 msec, $P < 0.005$) in 15 of 17 patients in whom these were attained.

Retrograde His-Purkinje and ventricular muscle refractoriness: Individual and mean values for retrograde refractoriness of the His-Purkinje system are presented in Table II and those for the ventricular myocardium in Table III. For the entire group of pa-

TABLE III

Ventricular Myocardial Refractoriness (in msec)

Case no.	CL	FRP of Ventricular Muscle C	FRP of Ventricular Muscle D	RRP of Ventricular Muscle C	RRP of Ventricular Muscle D	ERP of Ventricular Muscle C	ERP of Ventricular Muscle D
1	800	290	270	NA	NA	280	260
2	650	275	265	270	260	230	230
3	700	270	240	260	250	240	230
4	500	220	210	210	210	190	180
5	540	245	240	240	230	220	210
6	550	260	230	240	230	220	210
7	900	290	290	NA	NA	280	280
8	650	250	250	240	240	230	240
9	800	290	270	NA	NA	280	260
10	600	260	245	NA	240*	250	210
11	600	260	240	260	230	230	210
12	700	280	255	260	250	240	230
13	600	270	260	260	250	240	230
14	700	290	270	270	260	250	250
15	500	250	260	260	250	240	220
16	700	260	270	NA	NA	250	250
17	550	260	250	250	230	240	220
Mean ± SD		266 ± 19	254 ± 18	253 ± 17	240 ± 16	242 ± 23	231 ± 24
P value			<0.001		<0.001		<0.005

* Not included in the mean values.

C = control; CL = cycle length; D = digitalis (ouabain); ERP = effective refractory period; FRP = functional refractory period; NA = not attained; *P* = probability (difference from control value); RRP = relative refractory period; SD = standard deviation.

tients the retrograde functional refractory period of the His-Purkinje system was not significantly different after ouabain (469 ± 42 to 472 ± 39 msec, NS). This measurement increased by 5 to 35 msec in 7 of the 17 patients, remained unchanged in 6 patients and decreased by 5 to 15 msec in the remaining 4 patients (Table III). The retrograde effective refractory period of the His-Purkinje system could be determined in only four patients (Cases 2, 10, 16 and 17) during the control study. In the remaining 13 patients, the ventricular muscle became refractory before the effective refractory period of the His-Purkinje system was attained. In two of four patients (Cases 2 and 17) there was no change in the retrograde effective refractory period of the His-Purkinje system, whereas one patient (Case 10) showed a 10 msec increase and another (Case 16) a 10 msec decrease. In another four patients (Cases 3, 6, 13 and 15) the effective refractory period of the His-Purkinje system was attained only after ouabain; during the control study, it was limited by ventricular muscle refractoriness. The retrograde block in the His-Purkinje system seen in these four patients after ouabain was related to a retrograde V_2-H_2 gap phenomenon.

In contrast to the variable effects of ouabain on His-Purkinje system refractoriness, the functional refractory period (266 ± 19 to 254 ± 18, $P < 0.001$) and effective refractory period of the ventricular muscle (242 ± 23 to 231 ± 24 msec, $P < 0.005$) (range −10 to −40 msec) decreased significantly. Similarly there was a significant decrease in the relative refractory period of the ventricular muscle (253 ± 17 to 240 ± 16 msec, $P < 0.001$) in 11 of 12 patients in whom this value could be measured and compared during both control and post-ouabain studies.

Retrograde V_2-H_2 gaps: This phenomenon was observed in four patients during the control study, and

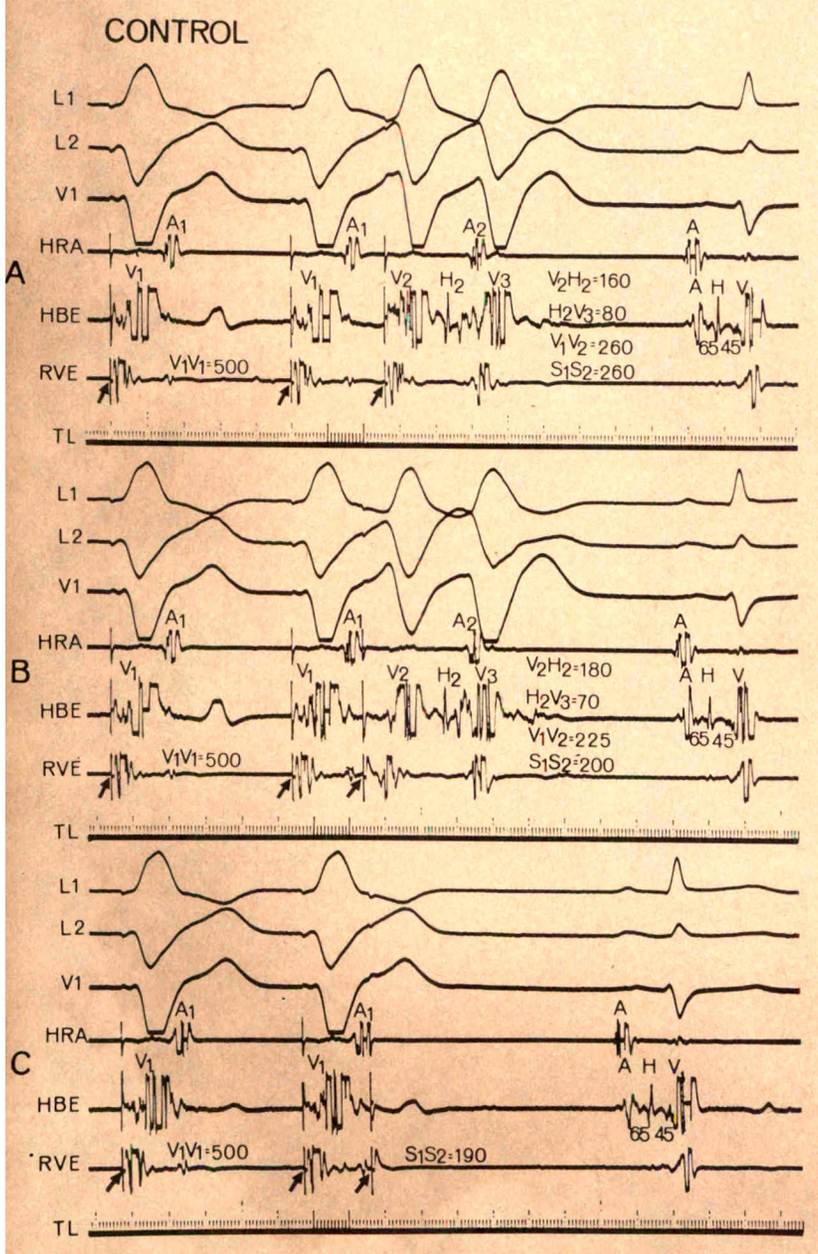


FIGURE 1. Patient 4. Control tracings. **From top to bottom in each panel,** L1, L2, V1 = surface electrocardiographic leads I, II and V_1, HRA = high right atrial electrogram, HBE = His bundle electrogram, RVE = right ventricular electrogram, and TL = time lines generated at 10, 100 and 1,000 msec. The basic ventricular cycle length (V_1-V_1) is 500 msec in all panels. **Panel A,** a premature stimulus (S_2) to the right ventricular myocardium is introduced at an S_1-S_2 interval of 260 msec. The premature ventricular depolarization (V_2) is conducted retrograde through the left bundle branch to the bundle of His with a V_2-H_2 interval of 160 msec, and V_3 follows with an H_2-V_3 interval of 80 msec. Note also that H_2 is followed by a retrograde A_2. The critical V_1-V_2 interval for reentry within the His-Purkinje system was 260 msec. **Panel B,** at an S_1-S_2 interval of 200 msec, latency between the premature stimulus artifact (S_2) and the V_2 electrogram results in a V_1-V_2 interval of 225 msec. The premature ventricular depolarization (V_2) is conducted retrograde with a V_2-H_2 interval of 180 msec (longer than in panel **A**), and V_3 follows with an H_2-V_3 of 70 msec (shorter than in panel **A**). The minimal V_1-V_2 interval for reentry within the His-Purkinje system was 225 msec, and the zone of reentry extended from 260 to 225 msec. **Panel C,** at an S_1-S_2 interval of 190 msec, the ventricular myocardium is refractory.

TABLE IV

Determinants of Intraventricular Reentry (in msec)

Case no.	CL	Zone of RE-HPS (V_1-V_2) C	Zone of RE-HPS (V_1-V_2) D	Critical V_2-H_2 For RE-HPS C	Critical V_2-H_2 For RE-HPS D	Maximal V_2-H_2 For RE-HPS C	Maximal V_2-H_2 For RE-HPS D	Range of H_2-V_3 For RE-HPS C	Range of H_2-V_3 For RE-HPS D
1	550	280-265	270-230	170	190	205	220	55-55	45-50
2	540	260-245	270-240	140	145	150	170	90-95	70-100
3	800	330-290	330-270	190	185	250	255	75-100	70-125
4	500	260-225	260-210	160	160	200	210	60-90	60-80
5	650	320-250	340-250	210	230	275	290	45-70	45-65
6	800	350-290	350-270	190	190	250	250	55-105	50-90
7	650	290-275	300-265	220	210	230	260	55-70	60-65
8	700	310-280*	270- -*	190	200	250*	-*	50-60*	60- -*
9	900	310-290	300-290	230	235	250	255	70-70	60-70
10	600	280-265*	245- -*	160	190	170*	-*	70-90*	50- -*
Mean ± SD		299 ± 30 to 266 ± 26	294 ± 36 to 253 ± 26	186 ± 29	193 ± 28	226 ± 40	239 ± 37	63 ± 14 to 82 ± 18	57 ± 9 to 80 ± 23
P Value			NS–< 0.025		NS		<0.01		NS–NS

* Not included in the means.

C = control; CL = cycle length; D = digitalis (ouabain); NS = not significant; *P* = probability; RE-HPS = reentry within His-Purkinje system; SD = standard deviation.

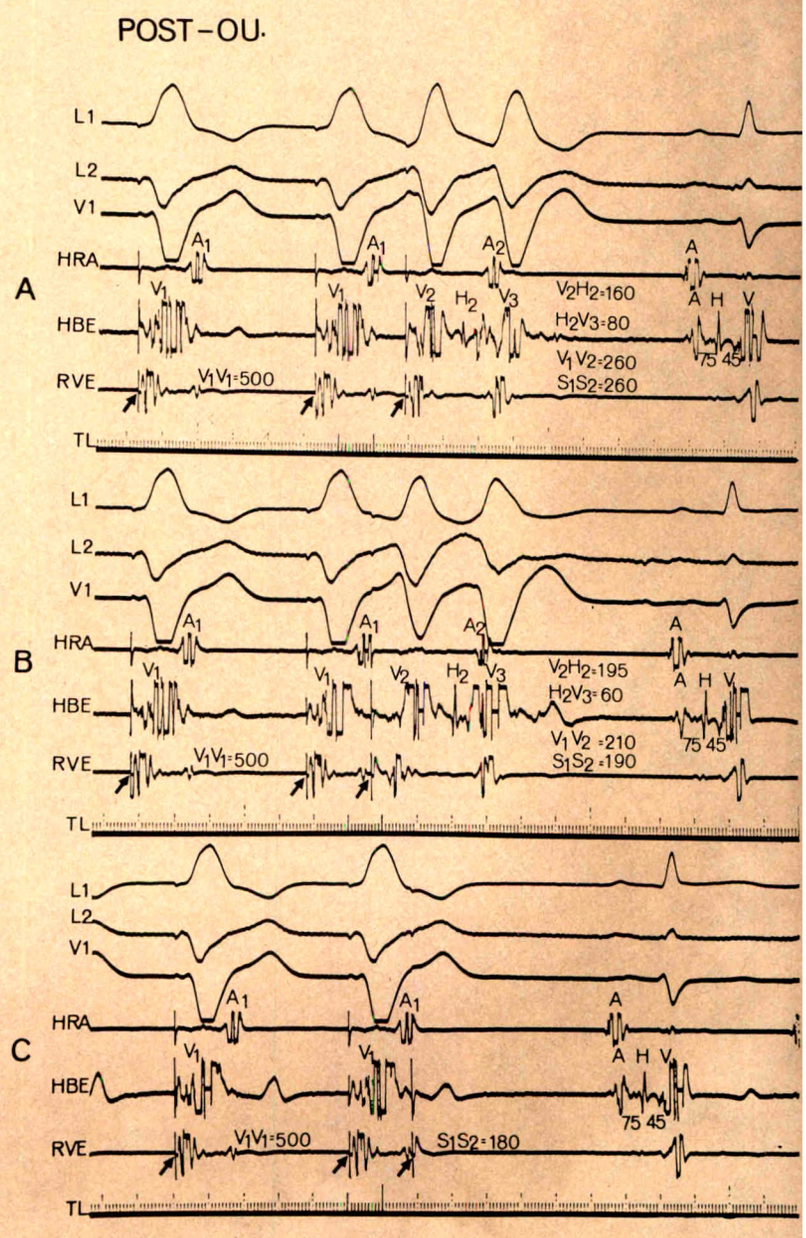


FIGURE 2. Patient 4. Tracings after ouabain (OU). The basic ventricular cycle length and abbreviations are as in Figure 1. **Panel A,** the critical V_1-V_2 interval (260 msec), critical V_2-H_2 interval (160 msec) and H_2-V_3 interval (80 msec) for reentry are similar to control values (Fig. 1, panel A). **Panel B,** at an S_1-S_2 interval of 210 msec, latency between the premature stimulus (S_2) and the local V_2 electrogram results in a V_1-V_2 interval of 210 msec. V_2 is conducted retrograde to the bundle of His with a V_2-H_2 interval of 195 msec, and V_3 follows with an H_2-V_3 interval of 60 msec. The minimal V_1-V_2 interval for reentry within the His-Purkinje system was 210 msec. Thus, after ouabain, the minimal V_1-V_2 and H_2-V_3 intervals were shorter than the control intervals, whereas the longest V_2-H_2 interval for reentry within the His-Purkinje system was longer than the control interval. The zone of reentry within the His-Purkinje system after ouabain extended from 260 to 210 msec and shifted to the left as a result of attainment of a shorter V_1-V_2 interval. **Panel C,** at an S_1-S_2 interval of 180 msec, the ventricular myocardium is refractory.

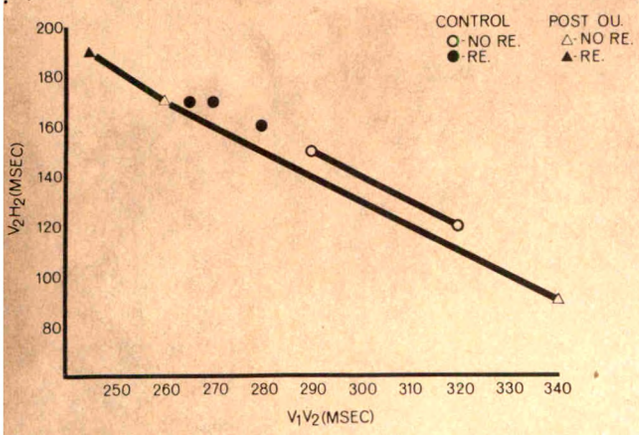


FIGURE 3. Patient 10. Demonstration of a decrease in the zone of reentry within the His-Purkinje system due to a retrograde His-Purkinje (V_2-H_2) gap. V_1-V_2 intervals are on the **abscissa,** V_2-H_2 intervals on the **ordinate.** During control studies (**circles**) at V_1-V_2 intervals of 310 msec and 300 msec, there is retrograde block (RE) in both bundle branches (V_2-H_2 gap, indicated by the **solid black line**). At V_1-V_2 intervals of 280 to 265 msec, retrograde conduction resumes and the corresponding V_2-H_2 delays are followed by reentry within the His-Purkinje system until the effective refractory period of the ventricular muscle is encountered. After ouabain (Post OU) (**triangles**), the V_2-H_2 gap zone extends from 330 to 270 msec. V_2-H_2 conduction resumes at a V_1-V_2 interval of 260 msec but is not associated with reentry. At a V_1-V_2 interval of 250 msec, V_2 again blocks in both bundle branches. As the V_1-V_2 interval is further decreased to 245 msec, retrograde conduction again resumes (V_2-H_2 = 190 msec) and a reentrant beat results. Note that the decrease in the zone of reentry after ouabain was primarily related to the extension of the V_2-H_2 gap zone.

the gap zone ranged from 10 to 90 msec (average 35 msec). After ouabain, gap zones increased in duration in three of four patients (range 25 to 80 msec; average 52.5 msec) (see Fig. 3). In another four patients (Cases 3, 6, 13 and 15) retrograde gaps occurred only after ouabain and ranged from 20 to 70 msec (average 47.5 msec).

Reentry

Reentry within the His-Purkinje system: This phenomenon was observed in 10 of 17 patients (58 percent) (Cases 1 to 10, Tables I and IV). This form of reentry was characterized by the occurrence of a reentrant beat (V_3) over a range of V_1-V_2 intervals and at critical V_2-H_2 delays; it generally persisted until the effective refractory period of the ventricular muscle was encountered. In 8 of 10 patients reentry occurred for a single beat whereas in two patients a second reentrant beat was observed at one or more coupling intervals.

Reentrant beats demonstrated the following characteristics: (1) The H-V intervals of the reentrant beats were longer than the H-V interval of the sinus beat, (2) the QRS configuration in lead V_3 was of left bundle branch block with left axis deviation, and (3) reentry terminated in the retrograde limb of the reentrant circuit (that is, V_3 was not followed by H_3). Table IV shows the individual and mean values of the determinants of reentry within the His-Purkinje system both before and after ouabain.

Zone of reentry: During control studies, the zone of reentry ranged from 15 to 70 msec. In 7 of 10 patients (Cases 1 to 7) the zone of reentry increased (36 ± 23 to 55 ± 23 msec, $P < 0.001$) after ouabain. Figures 1 and 2 are representative examples from Patient 4. In the remaining three patients (Cases 8 to 10) the zone of reentry decreased by 10 to 30 msec. In Patients 8 and 10, the decrease in the zone of reentry was due to a retrograde gap phenomenon in the bundle branch–His-Purkinje system (Fig. 3), whereas Patient 9 did not attain requisite V_2-H_2 delay for reentry at a V_1-V_2 interval of 310 msec (Table IV). In this patient only a 10 msec decrease in the zone of reentry was seen after ouabain.

V_1-V_2 and V_2-H_2 intervals for reentry within the His-Purkinje system: During the control studies, the average critical V_1-V_2 interval for reentry (outer limit of the reentry zone) was 299 ± 30 msec (range 260 to 350 msec). After ouabain, the average critical V_1-V_2 interval did not significantly differ from the control values (294 ± 36 msec, range 245 to 350 msec). However, the minimal V_1-V_2 interval for reentry (inner limit of the reentry zone) decreased significantly (266 ± 26 to 253 ± 26 msec, $P < 0.025$). The critical V_2-H_2 value at which reentry occurred was not significantly different from the control value (186 ± 29 to 193 ± 28 msec, NS) whereas the maximal V_2-H_2 value for reentry increased significantly after ouabain (226 ± 40 to 239 ± 37 msec, $P < 0.01$). In Patients 8 and 10 maximal V_2-H_2 intervals for reentry were not attained because reentry was confined to a 10 and 5 msec zone, respectively.

H_2-V_3 intervals of the reentrant beat: During the control studies the shortest H_2-V_3 intervals ranged from 45 to 90 msec (mean 63 ± 14 msec) and the longest H_2-V_3 intervals from 55 to 105 msec (mean 82 ± 18 msec). After ouabain, the H_2-V_3 intervals were generally shorter than control values, but the differences were not statistically significant (Table IV). No patient had sustained reentry after ouabain. Two patients who manifested V_4 during the control study, manifested it again after ouabain. In only one of eight patients was V_4 consistently observed after ouabain.

Discussion

Information concerning the direct effects of digitalis on the His-Purkinje system of the intact human heart is limited for several reasons. These include: (1) In most patients the functional refractory period of the A-V node exceeds the refractory period of the His-Purkinje system,[11,12] which in turn limits the atrial extrastimulus technique for study of the His-Purkinje system. (2) Digitalis itself increases the functional refractory period of the A-V node. In this study, the effects of ouabain on anterograde His-Purkinje refractoriness could not be assessed because in all patients the functional refractory period of the A-V node exceeded that of the His-Purkinje system.

Ouabain and retrograde His-Purkinje conduction and refractoriness: Our study confirms the value of the ventricular extrastimulus technique as a method of studying the His-Purkinje system and shows that digitalis has variable but insignificant effects on this system. Ouabain did not significantly change retrograde refractoriness as determined from measurements of

retrograde functional and effective refractory periods of the His-Purkinje system. Similarly, it did not affect retrograde His-Purkinje conduction, as determined from minimal V_2-H_2 intervals, or the V_1-V_2 intervals at which H_2 emerged from V_2. However, significantly longer maximal V_2-H_2 intervals were attained after ouabain. This effect was predominantly related to significant decreases in ventricular myocardial refractoriness, which allowed conduction to be measured at V_1-V_2 intervals shorter than with those of the control period.

In a study of the effects of digitalis on the A-V conduction system in 17 patients, Przybyla et al.[4] could obtain evidence in only 2 patients that digitalis did not change the effective refractory period of the His-Purkinje system. More recent observations[13] in the canine heart during His bundle stimulation revealed that therapeutic doses of ouabain had no effect on anterograde conduction within the His-Purkinje system but did increase anterograde His-Purkinje refractoriness in 7 of 12 dogs. This effect was small and statistically significant at long cycle lengths but insignificant at short cycle lengths. The apparent differences in the latter anterograde study in the dog and the current retrograde study in man may be related to (1) the use of different experimental models, because anterograde refractoriness may not correlate with retrograde His-Purkinje system refractoriness, (2) the use of different cycle lengths, and (3) species differences.

Ouabain and retrograde His-Purkinje gaps: Ouabain increased the duration of retrograde gap zones in three of four patients in whom these could be demonstrated during control studies. In addition, retrograde gaps occurred only after ouabain in 4 of 13 patients. The V_2-H_2 block in these patients could have occurred at one or more of these sites: ventricular muscle-Purkinje junctions, both bundle branches or the bundle of His. These effects of ouabain on retrograde gaps were presumably related to enhanced muscle conduction with resultant block in the Purkinje system. The observation that in three of four patients V_2-H_2 conduction resumed at even shorter V_1-V_2 intervals when the relative refractory period of the ventricular muscle was not yet attained suggests that conduction in the His-Purkinje system resumed subsequent to delay at a more proximal site in the His-Purkinje system but proximal to the initial site of block.

Ouabain and ventricular muscle refractoriness: In contrast to the variable and insignificant effects of ouabain on retrograde His-Purkinje system conduction and refractoriness, the drug decreased significantly all measures of ventricular muscle refractoriness and insignificantly decreased atrial muscle refractoriness. These effects on ventricular muscle are in agreement with previous observations in the intact canine heart[14,15] and may have a bearing on conduction across the A-V bypass tract in patients with Wolff-Parkinson-White syndrome. Wellens and Durrer[15] reported that ouabain decreased the anterograde refractory period of the bypass tract without significantly affecting the refractory period of atrial muscle. In contrast, Sellers et al.[16] reported that digoxin had variable effects on anterograde and retrograde refractory periods of the anomalous pathway. In neither of these studies were the effects of digitalis on the ventricular muscle reported. It is interesting to speculate that the increases in ventricular rate observed in some patients with the Wolff-Parkinson-White syndrome and atrial fibrillation who are given digitalis may be due to a decrease in refractoriness of either ventricular muscle or bypass tract, or both. Shortening of the refractory period of the ventricular muscle at the site of bypass insertion may in part be responsible for enhancement of conduction or less concealment, or both, giving rise to an increase in ventricular response.

Ouabain and reentry within the His-Purkinje system: Reentry has been postulated to be the mechanism for a variety of supraventricular[17–20] and some forms of ventricular arrhythmias.[21–25] The mechanism involved in the genesis of digitalis-induced ventricular arrhythmias although thought to be ectopic in origin remains unclear. Microelectrode studies[26,27] of Purkinje fibers exposed to ouabain and low potassium concentrations have revealed increased phase 4 depolarization with resultant enhanced automaticity in the setting of stretched Purkinje fibers, whereas low amplitude potentials or delayed after-depolarizations occur in undamaged fibers exposed to higher concentrations of potassium.These low amplitude potentials have been implicated in the development of the reentrant phenomenon.[27]

Reentry within the His-Purkinje system has been postulated to occur within a small microreentrant circuit[28,29] as well as over a large circuit involving the ventricular muscle and both bundle branches (macroreentry).[6–8] In either case the requisite conditions for the occurrence of reentry are unidirectional block, slow conduction and recovery of excitability. In this study, the effects of ouabain were assessed in the latter form of reentry. Ouabain modified but did not abolish the zone of reentry within the His-Purkinje system in 7 of 10 patients. The increase in the zone of reentry seen in these seven patients was predominantly due to a shift of the reentry zone to the left because the critical or longest V_1-V_2 intervals for reentry did not change after ouabain, whereas the minimal or shortest V_1-V_2 intervals for reentry decreased significantly. Shortening of the functional refractory period of the ventricular muscle after ouabain permitted the attainment of shorter V_1-V_2 intervals, which resulted in greater conduction delay in the left bundle branch and longer V_2-H_2 delays. In turn, longer V_2-H_2 delays allowed greater time for recovery of excitability of the right bundle branch and, thus, reentry occurred over a wider range of V_1-V_2 intervals.

In three patients the administration of ouabain was associated with a decrease in the zone of reentry by 25 to 30 msec in two patients and by 10 msec in the third patient. In the former two patients ouabain did not abolish unidirectional block or preclude attainment of requisite V_2-H_2 delays but created a bidirectional block. Bidirectional block in these patients may have occurred, singly or in combination at Purkinje-muscle junctions or in both bundle branches or in the bundle of His. The

observation that reentry did occur on further shortening of V_1-V_2 intervals suggests that delay at Purkinje muscle junctions or along the course of the left bundle (proximal delay with distal recovery) reinitiated reentry in these patients.

The shortest H_2-V_3 intervals of the reentrant beats decreased slightly but insignificantly after ouabain. This finding could be related to (1) a significant increase in maximal V_2-H_2 intervals because H_2-V_3 intervals may in part be determined by the length of V_2-H_2 intervals attained. A requisite delay in the left bundle branch conduction system may have allowed a greater degree of recovery of excitability of the right bundle branch-Purkinje system. (2) Because the percent decrease in the shortest H_2-V_3 intervals (−9.5 percent) was relatively greater than the percent increase in maximal V_2-H_2 intervals (+5.75 percent) for reentry it is also possible that, after ouabain, V_2 may have blocked in or penetrated less the proximal right bundle branch.

Clinical implications: (1) The observations made in this study suggest that digitalis has the propensity of sustaining reentry over a larger range of premature ventricular depolarizations. These effects of ouabain on reentry within the His-Purkinje system were related to the disparity in refractoriness between ventricular myocardium and the His-Purkinje system. (2) These digitalis effects on the His-Purkinje system are different from those reported for procainamide,[7,30] quinidine,[31] lidocaine[32] and diphenylhydantoin,[8] but the effects of digitalis on the ventricular myocardium are similar to those reported for lidocaine.[32] (3) We emphasize that most of our patients had a normal heart, and retrograde studies were performed at constant paced heart rates. Thus, it is difficult to make broad application of our data to the clinical setting of patients with a diseased heart in sinus rhythm or A-V block with long-term exposure to the therapeutic or toxic effects of the glycoside.

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Warnings and Precautions: Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients and such patients should be monitored by ECG for cardiac irregularities. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, **patients should be carefully directed to dissolve each dose completely in the stated amount of water.**

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

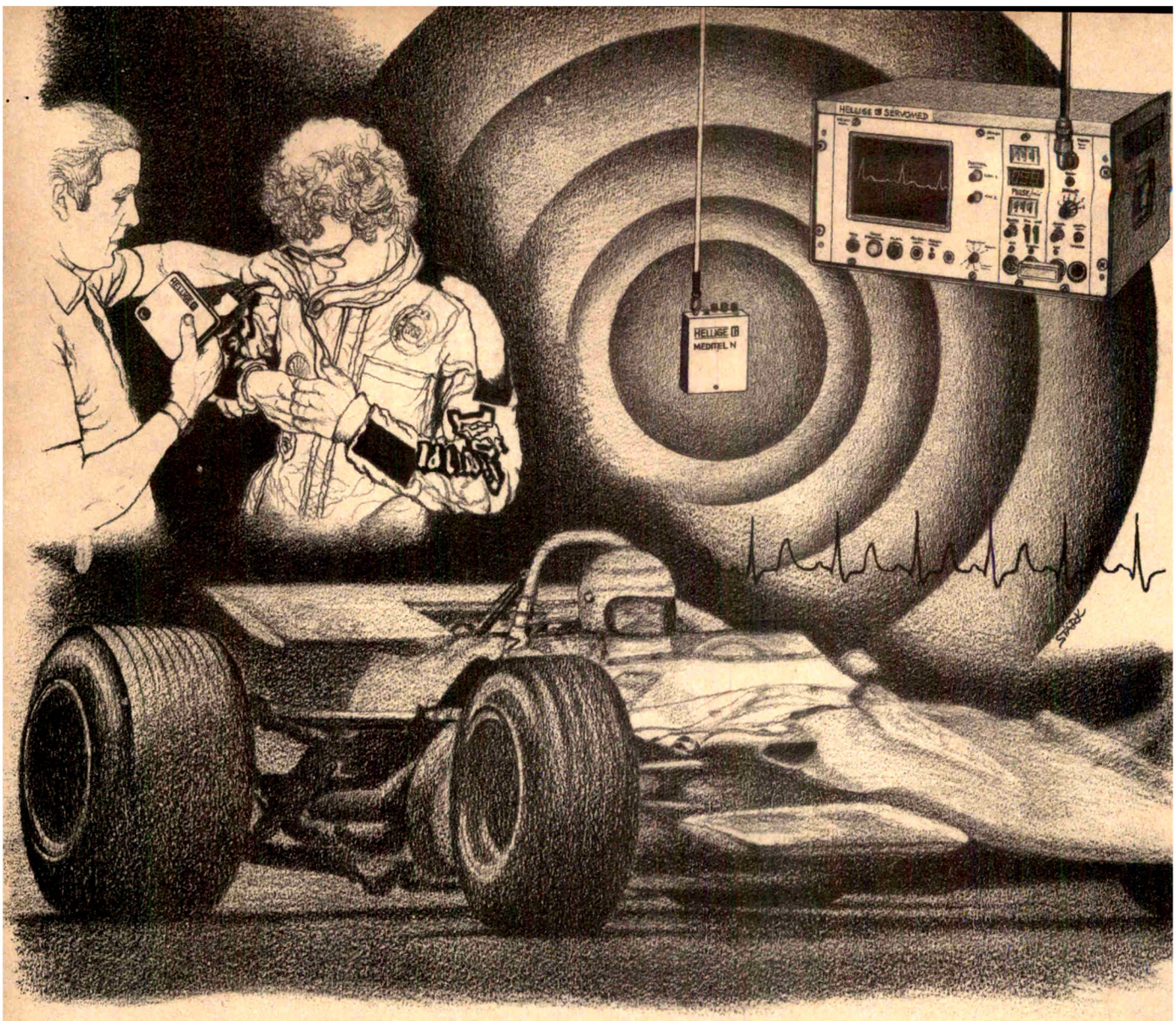
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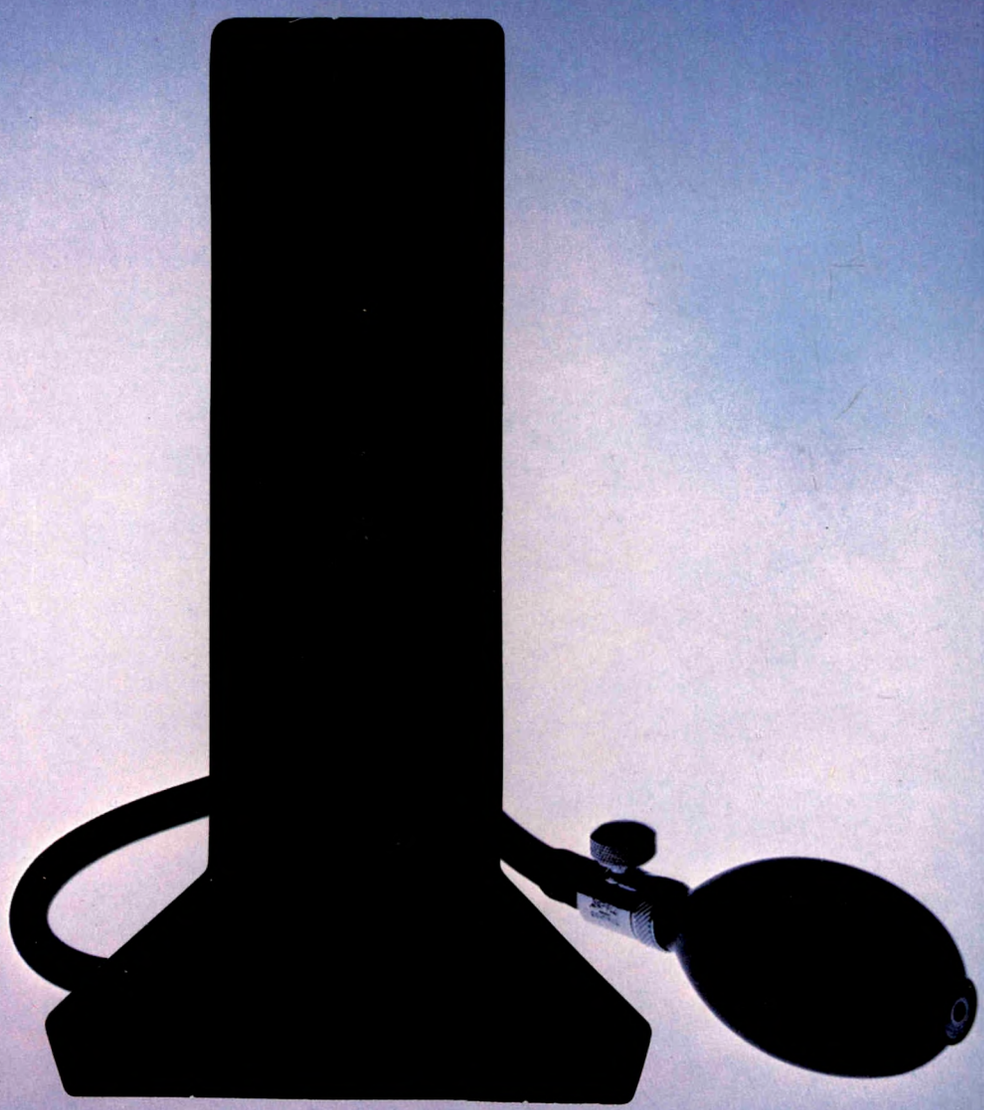
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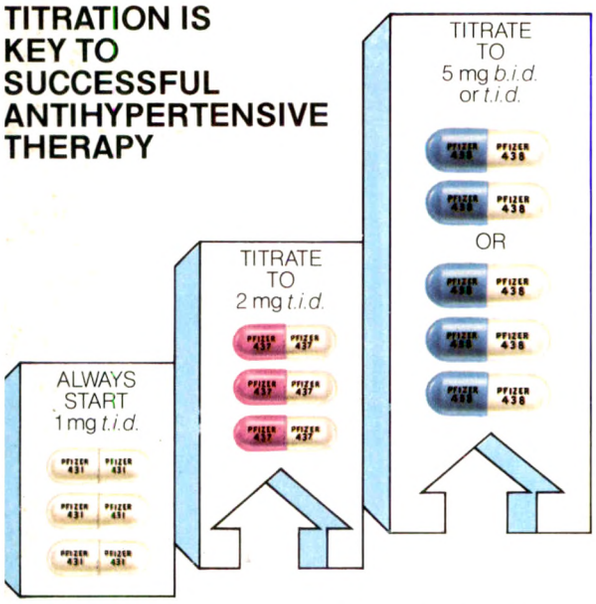
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Initial therapy: Whether using Minipress in ombination with other agents or alone, the start- g dosage is 1 mg *t.i.d.* If response is not adequate the next visit, the dosage should be increased 2 mg *t.i.d.*

Dosage titration: Thereafter, titrations of inipress should be carried out according to atient response. Dosage may be slowly increased a daily maximum of 20 mg given in divided oses. Although some patients may be controlled 1 mg *t.i.d.*, generally 6 mg to 15 mg daily will e needed in the majority of responding patients order to achieve optimal blood pressure control.

Maintenance therapy: After initial titration, atients may be maintained on a *b.i.d.* or *t.i.d.* osage regimen.

If optimum control is not achieved in patients eceiving Minipress and a diuretic, consider adding nother Step 2 antihypertensive agent.

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BRIEF SUMMARY

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INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug;occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit-dose institutional packages of 100 (10 x 10's).

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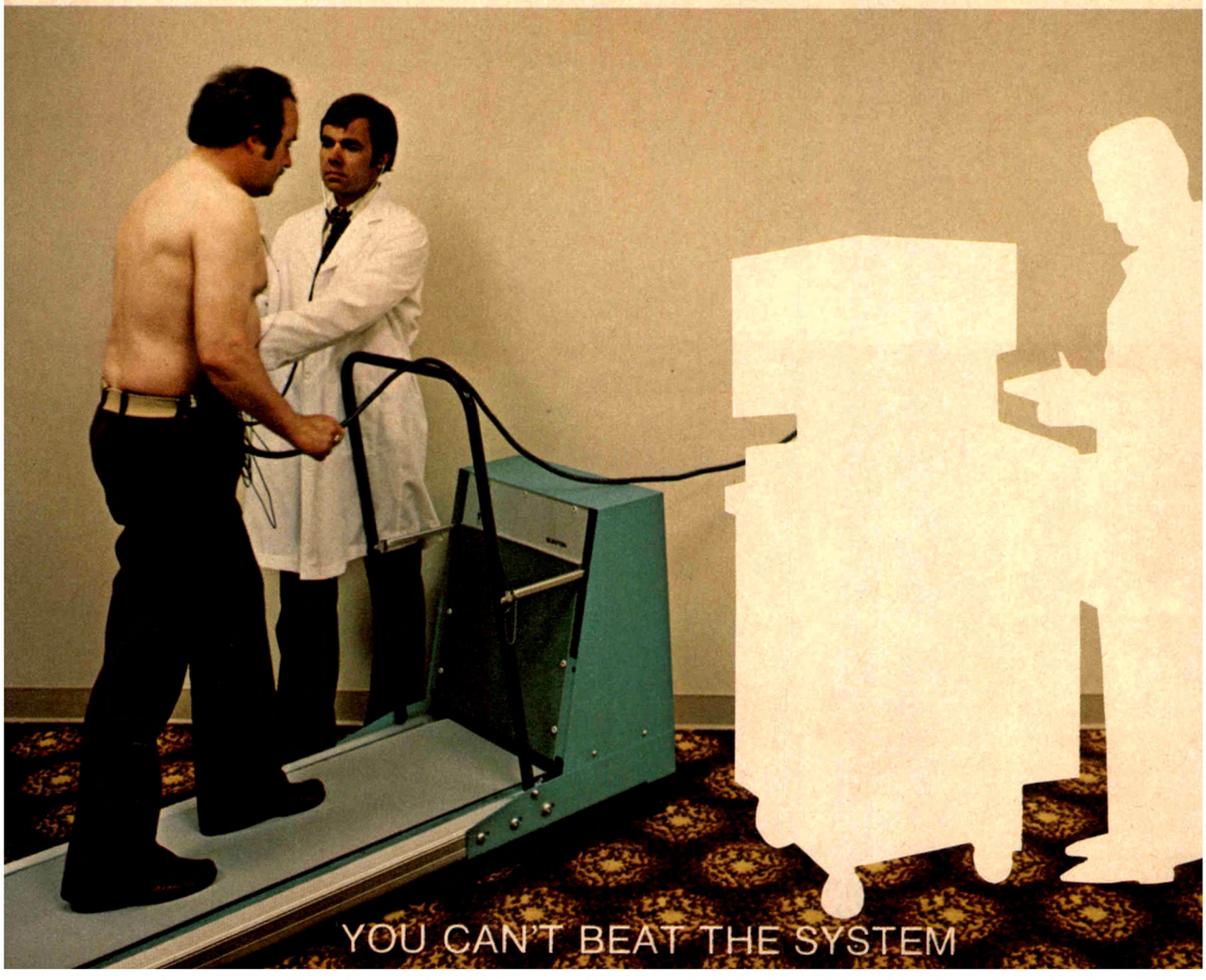
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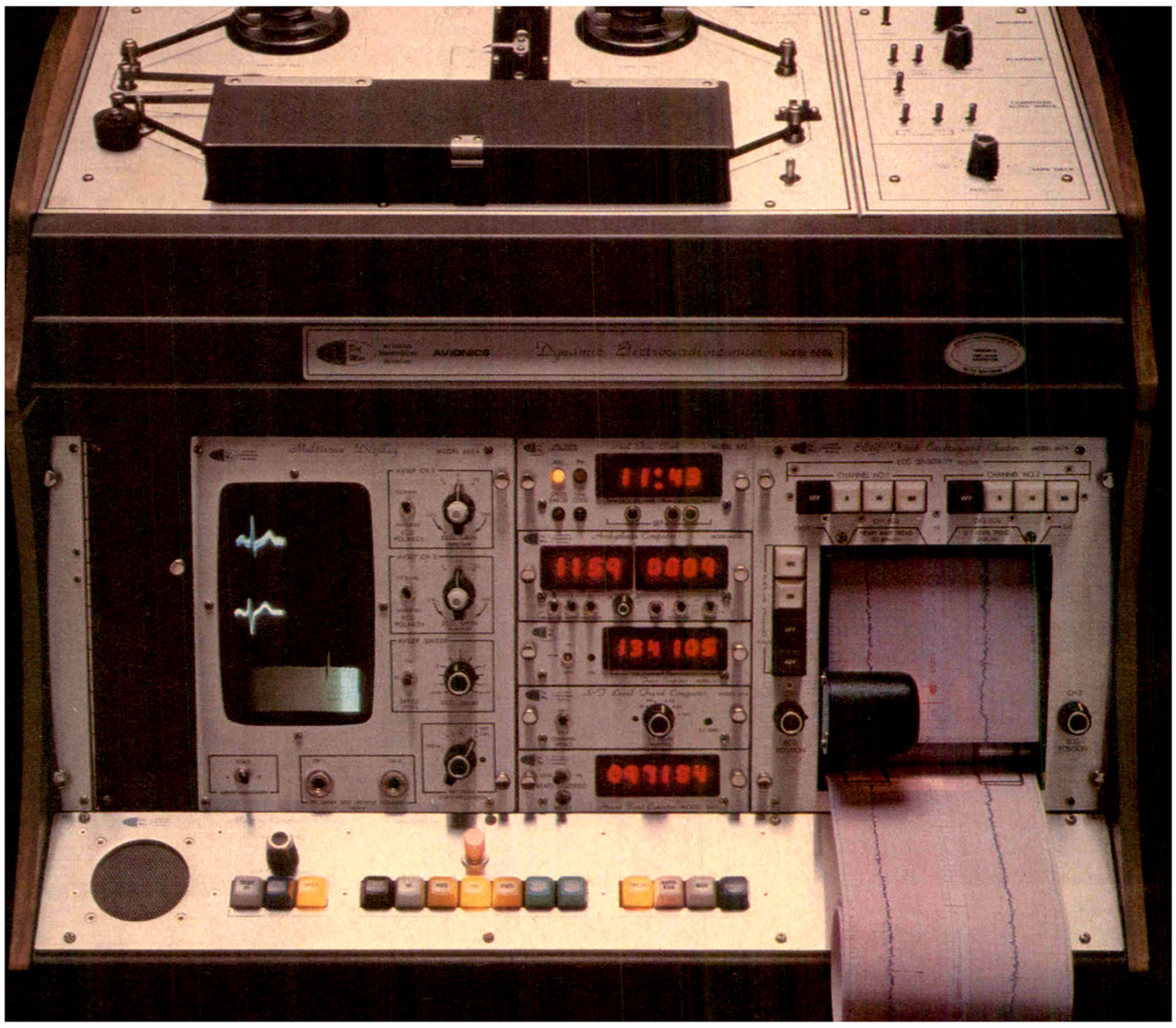
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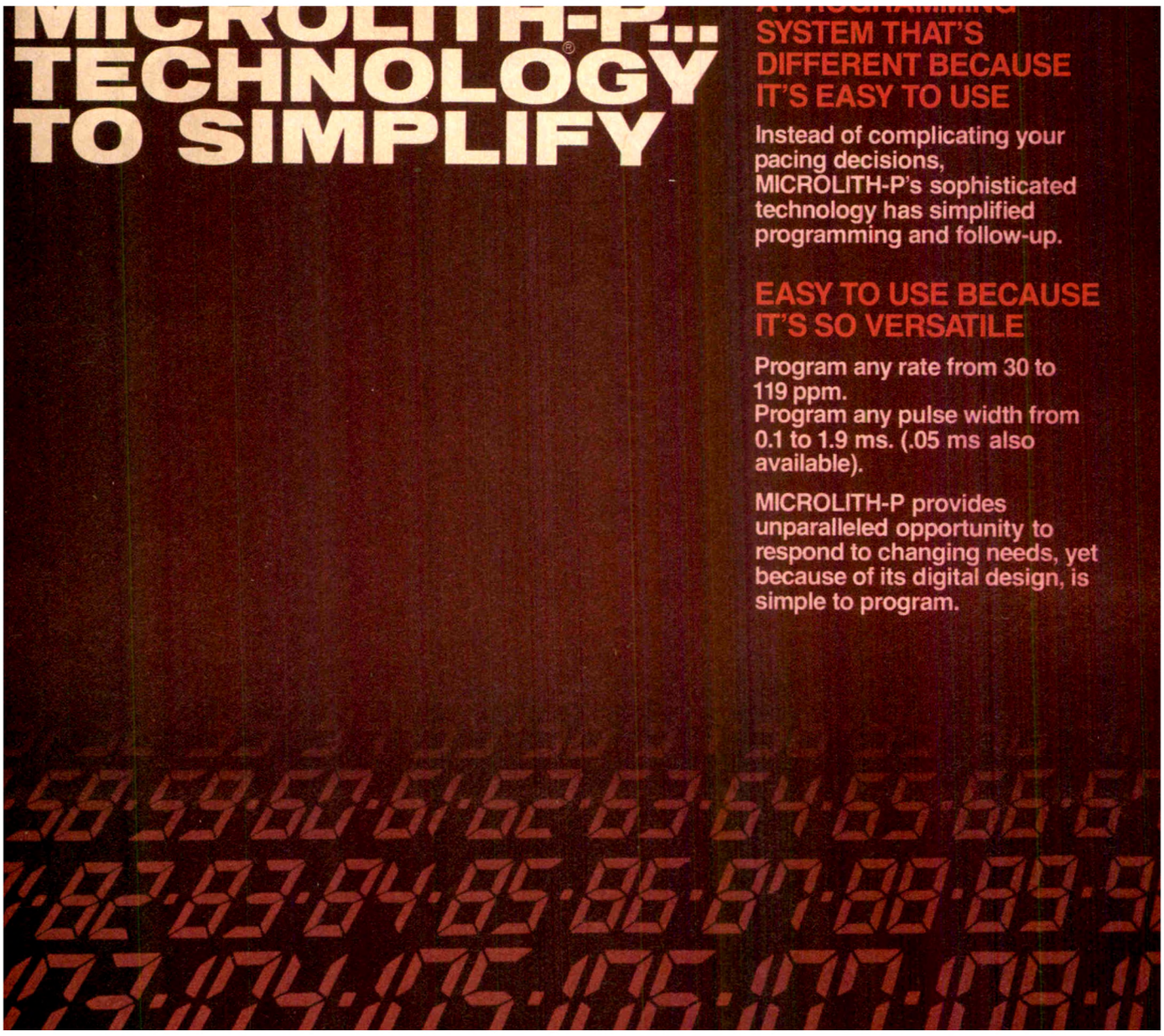
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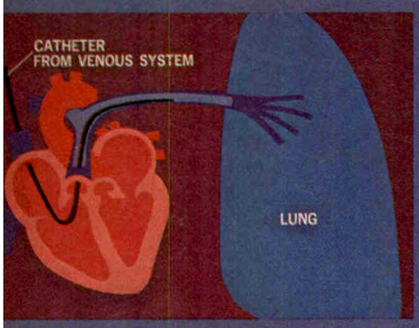
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New cardiac catheterization studies demonstrate prolonged changes for over 5 hours in cardiac hemodynamics with PERITRATE® 40-mg ORAL TABLET

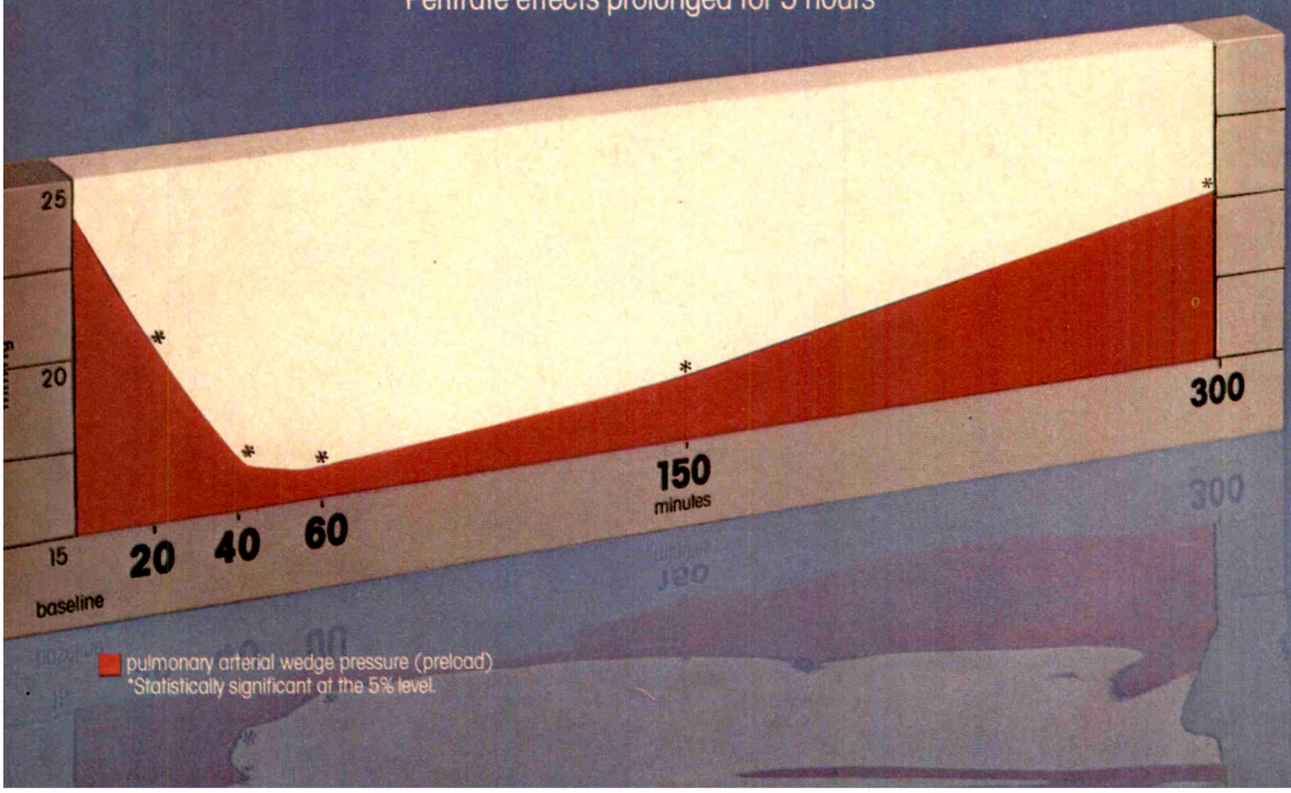
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A marked reduction in PRELOAD: Peritrate reduced pulmonary arterial wedge pressure for over 300 minutes. The maximum reduction was 37%. Pulmonary arterial mean pressure was also reduced for over 300 minutes. These manifestations of reduced PRELOAD resulted from an increase in venous capacitance leading to a reduction in left ventricular end-diastolic volume and pressure. The observed reduction in pulmonary wedge pressure indicates marked preload reduction.

Peritrate effects prolonged for 5 hours



A reduction in AFTERLOAD: A significant reduction of arterial blood pressure, correlating with reduced AFTERLOAD, was maintained for over 300 minutes.[1]

Reduction in blood pressure for 5 hours

parameter	before Peritrate n=12	60 minutes after Peritrate n=12	150 minutes after Peritrate n=12	300 minutes after Peritrate n=8
blood pressure (mmHg) systolic	122.6	116.7*	116.9	116.8
diastolic	68.7	63.4*	61.3*	61.0*

*Statistically significant at the 5% level.

Peritrate actions observed

- Activity was prolonged for at least 5 hours.
- PRELOAD and AFTERLOAD showed a marked reduction lasting at least 5 hours.

1. Klein RC, Amsterdam EA, Pratt C, et al: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy. Presented at The American Federation for Clinical Research, San Francisco, Calif, April 29-May 1, 1978.

Please see following page for brief summary of prescribing information.

Conclusions

1. The prolonged reduction in preload and afterload reduces the amount of energy expended and oxygen consumed by the hea This reduction in oxygen demand should relieve or prevent angina.
2. Provides a smooth onset of action without tachycardia. Unwanted effects are rare, and patient compliance is excellent.

PERITRATE® 40 mg
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CAUTION: Federal law prohibits dispensing without prescription.
Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg–double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

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Electrograms From the Canine Sinoatrial Pacemaker Recorded in Vitro and in Situ

MARVIN CRAMER, MD
ROBERT J. HARIMAN, MD
ROBERT BOXER, MD
BRIAN F. HOFFMAN, MD

New York, New York

We have identified extracell potential changes associated with t electrical activity of the canine sinoatrial pacemaker. Small nonpolarizal electrodes and low frequency high gain amplification were used to rec unipolar electrograms from both the epicardial and the endocardial s faces of the canine sinus node. Initially in vitro studies were perform so that transmembrane action potential changes could be recorded multaneously with the extracell potentials. The sinus nodal electrogr showed two characteristic potentials when the electrode was in immedi proximity to pacemaking cells: (1) During phase 4 there was a stea slope of about −30 to −100 μv/sec, and (2) during the transition fr phase 4 to phase 0 of the transmembrane action potential the slope of t electrogram increased smoothly to approximately −400 to −1,0 μv/sec. These potentials were followed by high frequency deflections cells in the surrounding atrium depolarized. Tetrodotoxin (5 mg/lit rendered the atrial muscle inexcitable and delayed and then abolish the high frequency activity in the sinus electrogram, which then appea as a continuous smooth tracing similar to the sinus pacemaker acti potential but reversed in polarity. We then recorded these small localiz potentials from the in situ canine heart. Sinus nodal electrograms co be obtained from beating hearts with hand held probes on the epicard surface and with conventional recording catheters on the endocard surface. The results demonstrate that the canine sinus node gives r to detectable and characteristic changes in extracell potential a suggest that similar potentials can be recorded from man to evalu sinus nodal function.

Until recently, attempts to record electrograms of the sinus pacema of mammalian hearts have produced records that varied in configurat and were difficult to interpret.[1–5] Both low and high frequency potent preceding early atrial depolarization have been recorded from the a of the sinus node, but proof that such potentials originate in true pa maker cells has been lacking. Recently,[6] we showed that with use of h gain direct coupled amplification it is possible to record an extra electrogram that shows the electrical activity of the sinus pacemake an isolated preparation of rabbit atrium.

This paper extends these observations to provide evidence that sim extracell complexes can be recorded from the canine sinus node both vitro and in situ. The in vitro studies used simultaneous microelectr recordings from a canine right atrial preparation to demonstrate c relations between transmembrane and extracell potentials. The exp iments on the in situ heart were performed to determine the feasibil of recording these small localized potentials from intact hearts.

We believe that our results clearly show that the canine sinus no a structure closely resembling the human sinus node, gives rise characteristic extracell potentials that can be recorded through app

From the Departments of Pharmacology and Medicine, College of Physicians and Surgeons, Columbia University, New York, New York. This study was supported by Grants HL-08508-14, HL-07271-01 and HL-12738-10 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received April 17, 1978; revised manuscript received June 26, 1978, accepted July 5, 1978.

Address for reprints: Brian F. Hoffman, MD, Department of Pharmacology, College of Physicians & Surgeons, Columbia University, 630 West 168th Street, New York, New York 10032.

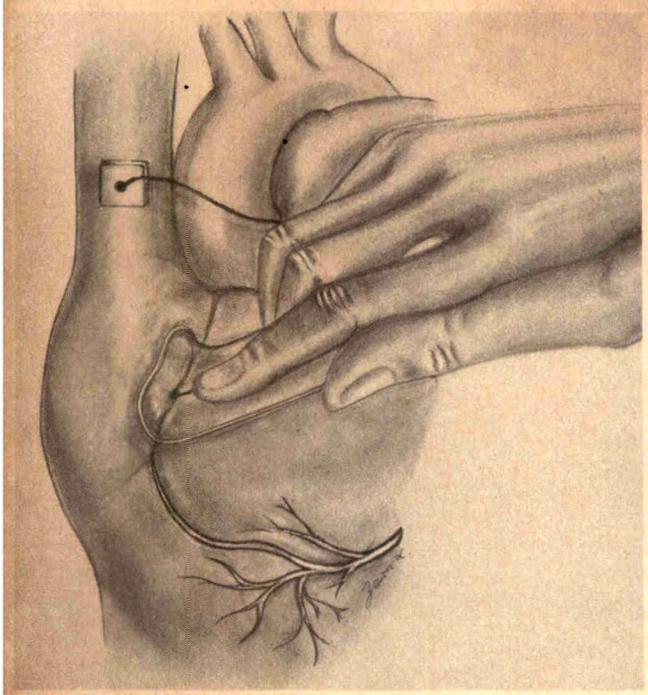


FIGURE 1. Drawing of the hand-held electrode used in obtaining epicardial electrograms from the in situ heart. See text for details.

priate leads. These potentials are produced by membrane currents of sinus pacemaker cells and thus provide an extracell electrogram truly representative of electrical activity of the sinus pacemaker.

Methods

In Vitro Experiments

Experimental preparation: Young adult mongrel dogs (5 to 9 kg) were anesthetized with sodium pentobarbital (30 mg/kg intravenously). The hearts were removed through a right thoracotomy and placed in cooled Tyrode's solution. Isolated preparations of right atrium containing the sinus node, sinus nodal artery and right coronary artery were dissected free from the rest of the heart according to the methods described by Woods et al.[7] A catheter was placed in the right coronary artery near the origin of the sinus nodal artery, and distal branches of the right coronary artery were ligated. The preparation was pinned in a wax tissue bath and both superfused (10 ml/min) and perfused through the catheter at a constant pressure of 36 mm saline solution with Tyrode's solution warmed to 36 to 37 °C and saturated with 95 percent oxygen and 5 percent carbon dioxide (pH −7.3). The composition of the Tyrode's solution (in millimoles) was as follows: sodium chloride, 137; potassium chloride, 4.0; calcium chloride, 2.7; $NaHCO_3$, 12.0; $NaHPO_4$, 0.5M; magnesium chloride, 0.5; glucose, 5.5. For some experiments tetrodotoxin, 2 to 10 mg/liter, was added to the Tyrode's solution. Heart rates ranged from 48 to 82 beats/min.

Recording techniques: Conventional microelectrode techniques were used to record transmembrane potentials. Microelectrodes filled with 3 molar potassium chloride were coupled to amplifiers with high input impedance and capacity neutralization through silver-silver chloride junctions. A ramp signal of 100 mv and 0.5 msec duration was injected between the bath and ground to calibrate the gain and frequency response of these amplifiers. Because the preparation contracted vigorously and the microelectrodes were mounted rigidly, only a few satisfactory transmembrane action potentials could be recorded during each impalement.

The extracell potentials were recorded in a manner similar to that described previously.[6] The electrodes were matched silver-silver chloride rods 0.5 mm in diameter and insulated to the tip with polyethylene. They were connected to a Tektronix 3A9 preamplifier. Originally, records were obtained with only direct current amplification but alternating current amplification also was used. Several time constants were tested. Band pass filters of 0.1 and 100 hertz provided undistorted recordings of the sinus nodal potentials while minimizing drift and reducing the amplitude of high frequency potentials generated by atrial muscle. The electrodes were chlorided before each experiment and were free of drift at gains of 50 μv/cm. A unipolar recording mode was used with the indifferent electrode located at the periphery of the bath. The record of change in extracell potential was calibrated by signals of 50 to 100 μv/sec delivered by a separate calibrator.

Both the intracell and extracell electrodes were mounted in micromanipulators and positioned over the tissue with the help of a binocular dissecting microscope. Simultaneous extracell and transmembrane recordings were recorded from the epicardial surface of the sinus node. Extracell potentials also were recorded from the endocardial surface. However, like Woods et al.,[7] we were unable to impale pacemaker cells from the endocardial side. The extracell electrode was held about 5 mm from the surface of the preparation. The microelectrode was mounted at an angle so that it could be advanced under the edge of the extracell electrode. Teflon®-coated silver wires, 0.1 mm in diameter, were used to record a bipolar atrial electrogram that served as a time reference. The records were displayed on a Tektronix 565 oscilloscope and recorded with a Gould Brush recorder at speeds of 5 to 50 mm/sec.

In Situ Experiments

Adult mongrel dogs (10 to 22 kg) were preanesthetized with morphine sulfate (2 mg/kg intramuscularly) and anesthetized with chloralose (300 mg/kg intravenously). Heart rates ranged from 66 to 148 beats/min. The heart was exposed through a right thoracotomy in the third intercostal space, and a pericardial cradle was constructed.

Epicardial sinus nodal recording: Sinus nodal potentials were recorded from the epicardial surface of the node using several hand-held probes. The initial experiments used the same silver-silver chloride rod electrodes used for the in vitro experiments. These provided satisfactory records but were difficult to hold in a fixed position on the surface of the heart and tended to traumatize the tissue at the recording site. We also experimented with conventional exploring probes of the type used in recording His bundle potentials during open heart surgery.[8] This type of electrode was difficult to place precisely over the linea terminalis because small anatomic details could not be identified through the thick plexiglass head of the probe. The most satisfactory electrode was similar to electrodes Dobelle et al.[9] have used for long-term implantation over the occipital lobe in man. It consisted of a platinum electrode, 1 mm in diameter, mounted flush in a piece of flexible transparent Teflon® (Fig. 1). We were able to hold this electrode over the pacemaking site for several minutes at a time without trauma or movement artifact. The exploring electrode was matched to an indifferent electrode that was sewn to the superior vena cava 3 to 5 cm superior to the linea terminalis. This distance permitted the electrode pair to function as a "unipolar" system with respect to the weak and localized sinus nodal potentials but as a bipolar pair for more

distant electrical activity. Thus it emphasized activity around the sinus region while tending to minimize potentials from the rest of the heart.

Endocardial sinus wall recording: In some experiments, after the pacemaking site had been localized on the epicardial surface, a no. 4F recording catheter (Cordis 370-122) was introduced by way of the right jugular vein and positioned near the same site on the endocardial surface. The catheter usually could be held in a stable position for several minutes at a time. The distal electrode on the catheter functioned as the exploring electrode and the proximal one as the indifferent electrode (the interelectrode distance was 15 mm). The signals from the in situ experiments were amplified with an Electronics for Medicine DR 8 recorder and recorded on film at speeds of 50 to 100 mm/sec. Filter settings of 0.1 to 50 hertz were used.

Results

In Vitro Records

Characteristics of the electrogram and localization of the pacemaker: We began the experiments by exploring the epicardial surface along the linea terminalis with the extracell electrode searching for extracell potentials like those we had recorded[6] from the primary pacemaking area of the rabbit heart. We were consistently able to locate an area less than 2 mm^2 along the linea that yielded such potentials. Figure 2 shows transmembrane and extracell potentials recorded from such an area in three different preparations. The top recordings are transmembrane potentials, the middle tracings high gain extracell electrograms recorded from the same sites, and the bottom tracings bipolar atrial electrograms that provide a time reference. To facilitate comparisons between transmembrane and extracell recordings the polarity of the extracell electrogram is reversed from the usual electrocardiographic convention so that a wave of depolarization approaching the exploring electrode leads to a downward deflection. In each record there is a consistent relation between the

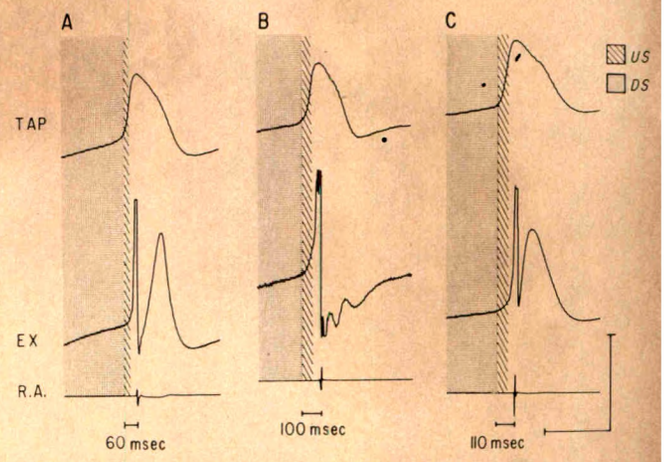


FIGURE 2. Transmembrane potentials (TAP) (**top tracings**) and extracell (EX) electrograms (**middle tracings**) from the pacemaking region in three isolated canine sinus node preparations. The **bottom tracings** are bipolar right atrial (R.A.) electrograms that serve as time references. The **vertical bar** corresponds to 75 mv in the transmembrane records and 100 μv in the extracell electrograms. The **horizontal bar** equals 400 msec. DS = diastolic slope; US = upstroke. See text for details.

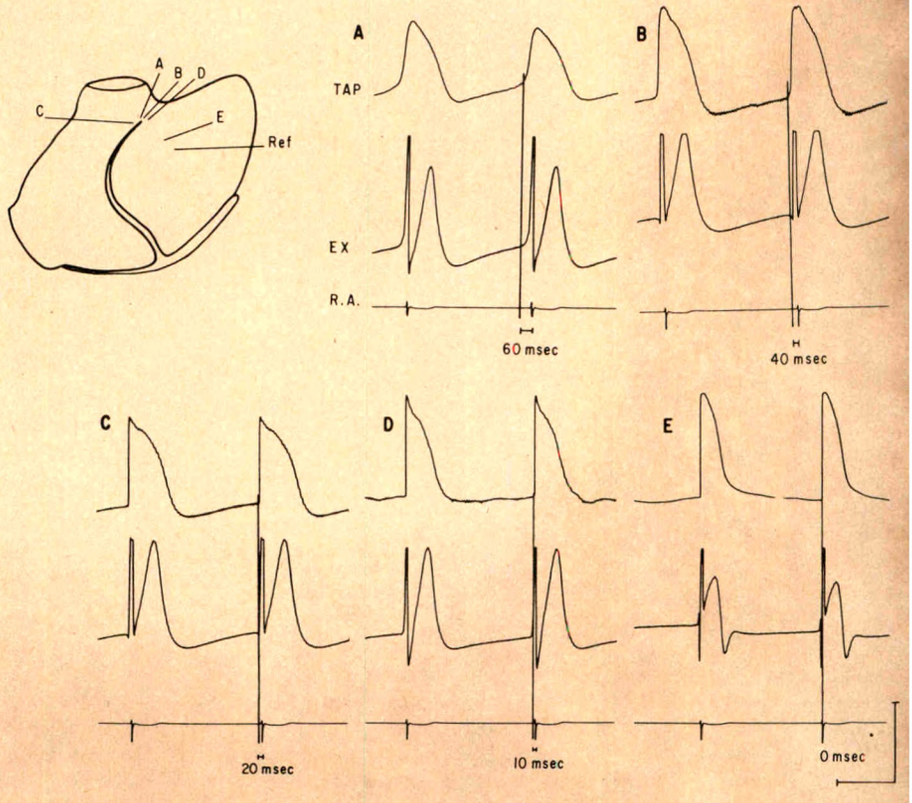


FIGURE 3. Examples of transmembrane and extracell potentials from other regions of the sinus node and atrium. The **upper tracing** is a transmembrane potential (TAP), the **middle** an extracell (EX) electrogram from the same site, and the **lower** a reference right atrial (R.A.) electrogram held constant throughout. The locations of each record are indicated in the drawing at **upper left.** The **vertical bar** corresponds to 75 mv in the transmembrane records and 100 μv in the extracell electrograms. The **horizontal bar** equals 400 msec. Ref = reference. See text for details.

transmembrane and extracell potentials. During phase 4 of the transmembrane potential a steady slope of −30 to −100 μv/sec is recorded extracellularly. Then, as the transmembrane potential shows the transition from phase 4 to phase 0, the external potential shifts to a much steeper slope of −400 to −1,000 μv/sec. This slow potential then is interrupted by high frequency changes as cells outside the pacemaking region are depolarized. The remainder of the extracell record is very variable. We have termed the extracell potential associated with phase 4 the *diastolic slope* and the potential associated with the onset of phase 0 the *upstroke slope*.[6] Several features of the complex deserve particular emphasis. First, as mentioned, it can be recorded only from a small area on the linea terminalis. Transmembrane potentials characteristic of true pacemaking cells were always found at this site. Also, this complex is essentially indistinguishable from the record we previously have obtained from the primary pacemaking region of the rabbit sinus node.

Extracell potentials recorded from other areas around the sinus node are more variable. Figure 3 shows examples of potentials recorded from several sites in the same preparation. For each location records of the extracell and transmembrane potentials are shown as well as an atrial electrogram as a time reference. Panel A is recorded from the primary pacemaking region. Panels B and C are recorded from other sites along the linea terminalis. Here the transmembrane potentials demonstrate diastolic depolarization but the transition from phase 4 to phase 0 is more abrupt and occurs much later than phase 0 depolarization in the primary pacemaking region. The extracell records show diastolic slopes suggesting phase 4 depolarization is occurring in the cells underneath the electrode. However, no upstroke slope is seen. Instead, the diastolic slope is interrupted by an initial positive deflection beginning before the cells under the electrode are depolarized. Extracell complexes of this type are similar to those recorded from latent pacemaking areas of the rabbit sinus node. Panels D and E are both recorded from atrial muscle caudal to the linea. Panel D is recorded only 4 mm from the pacemaking site and does show a faint diastolic slope. However, when the electrode is 10 mm from the crista (panel E) no change in potential is seen during diastole.

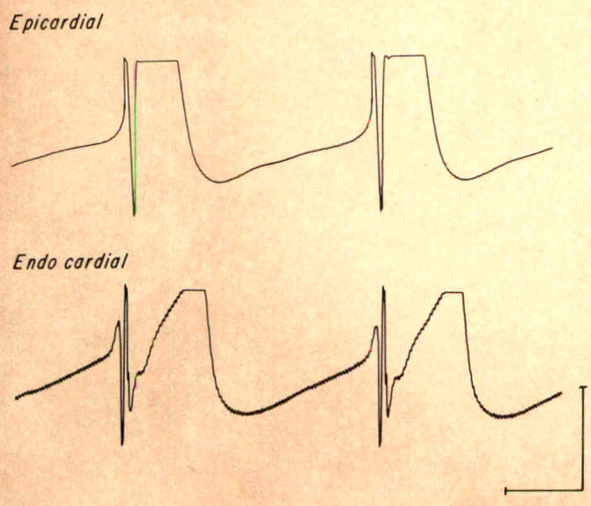


FIGURE 4. Extracell electrograms from both the epicardial and endocardial surfaces of the sinus pacemaker in an isolated preparation. The **vertical bar** corresponds to 100 μv and the **horizontal** to 400 msec. See text for details.

Electrograms from the endocardial surface: To determine if extracell potentials from the sinus pacemaker could be recorded from the endocardial surface, the preparations were turned and remounted with the endocardial surface uppermost. The location of the pacemaker was marked by driving a pin through the atrium a few mm cephalad to it. Figure 4 demonstrates potentials recorded from epicardial and endocardial surfaces of the sinus pacemaker. The complexes are essentially identical and both show typical diastolic and upstroke slopes.

Effects of tetrodotoxin: To demonstrate that the two types of potentials recorded over the canine sinus pacemaker were due, respectively, to phase 4 and phase 0 depolarization of pacemaker cells, we repeated one of the confirmatory experiments previously performed in the rabbit heart. In those studies the fast sodium ion channel blocker tetrodotoxin abolished all activity in the atrium without affecting the sinus pacemaker and permitted a clear identification of low and high frequency potentials in the sinus electrogram.[6] Figure 5 demonstrates the effect of tetrodotoxin (5 mg/liter) on the extracell potentials produced by the canine sinus pacemaker. Figure 5A shows control records of a transmembrane potential and extracell electrogram recorded from the sinus pacemaker and a reference atrial electrogram recorded through electrodes positioned just beyond the linea. After beginning the tetrodotoxin perfusion, conduction velocity in the fast sodium ion-dependent tissues slows. Figure 5B is recorded 10 minutes after the start of tetrodotoxin administration. The microelectrode has been dislodged at this time. In the electrogram the high frequency deflections are beginning to separate from the diastolic and upstroke slopes. The time from sinus depolarization, as indicated by the onset of the upstroke slope, to atrial depolarization has lengthened from 100 to 200 msec. Figure 5C shows the development of complete sinoatrial block as it appears in the sinus electrogram. For the first cycle, the time from the upstroke slope to atrial depolarization is 220 msec. The second lengthens to 240 msec, and the third sinus depolarization fails to propagate out of the pacemaking region. No activity is recorded by the reference atrial electrogram and no high frequency deflections are present in the sinus electrogram. The preparation was maintained in complete sinoatrial block until a sinus pacemaker cell could be impaled. Figure 5D shows transmembrane and extracell potentials recorded at a rapid sweep speed. The extracell potential is a smooth continuous tracing opposite in polarity but similar in shape to the transmembrane action potential. Temporal correlations between phases 4 and 0 and the diastolic and upstroke slopes are maintained. All the effects of tetrodotoxin were reversed on return to a drug-free medium.

In Situ Records

Localization of the pacemaker: Success in recording sinus nodal potentials from the in situ heart requires that the exploring electrode be held in stable position precisely over the sinus pacemaker. Figure 6 is an example of a typical sinus nodal electrogram recorded from the epicardial surface of the in situ canine heart with a hand-held probe. A surface lead II electrocardiogram and an electrogram from the right atrial appendage also are shown. The sinus nodal electrogram shows diastolic and upstroke slopes like those recorded

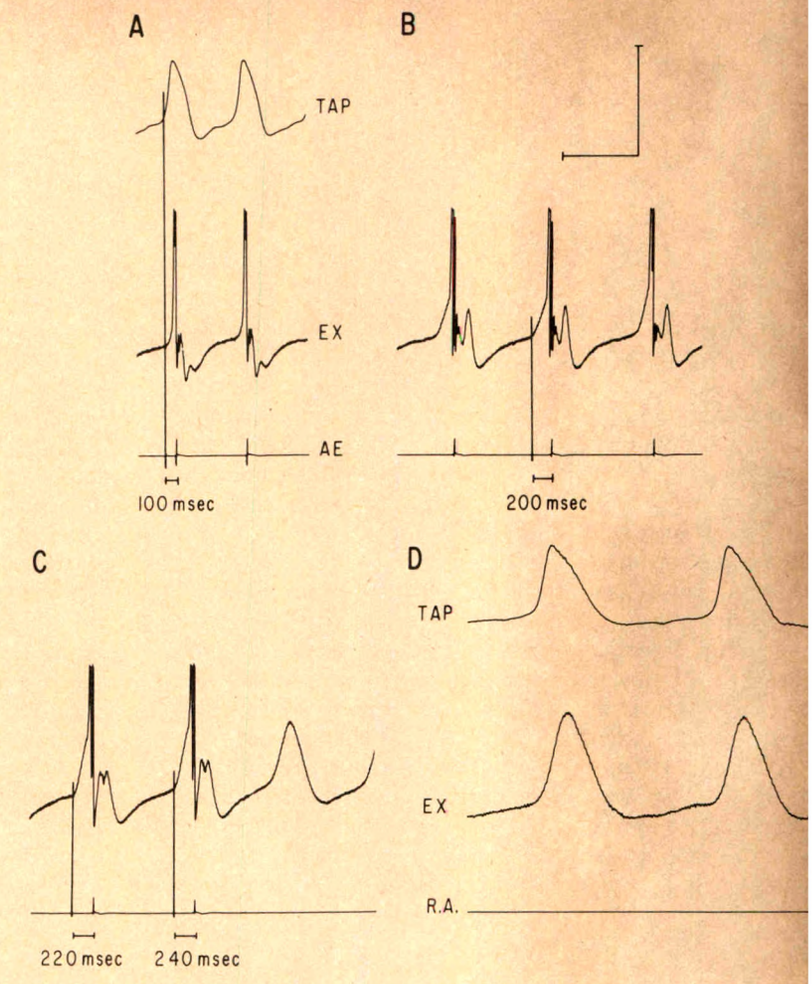


FIGURE 5. The effects of tetrodotoxin on the sinus nodal electrogram. **A** and **D** show transmembrane potentials (TAP) **(upper tracings)** and extracell electrograms (EX) **(middle tracings)** from the sinus pacemaker together with a reference right atrial electrogram (AE and R.A.) The microelectrode was dislodged during **B** and **C**. **D** is recorded at a sweep speed of 50 mm/sec to emphasize relations between transmembrane and extracell potentials. The **vertical bar** corresponds to 80 mv in the transmembrane records and 100 μv in the sinus electrogram. The **horizontal bar** equals 200 msec in **A**, **B** and **C** and 400 msec in **D**. See text for details.

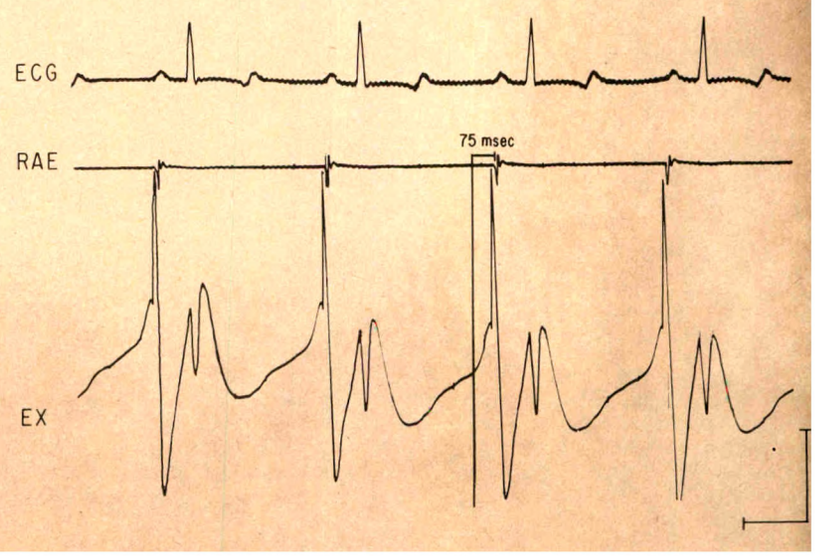


FIGURE 6. Sinus nodal electrogram (EX) from the epicardial surface of an in situ heart. A lead II electrocardiogram (ECG) and right atrial electrogram (RAE) are also shown. High frequency components of the sinus electrogram have been retouched for clarity. The **vertical bar** corresponds to 100 μv and the **horizontal** to 200 msec. See text for details.

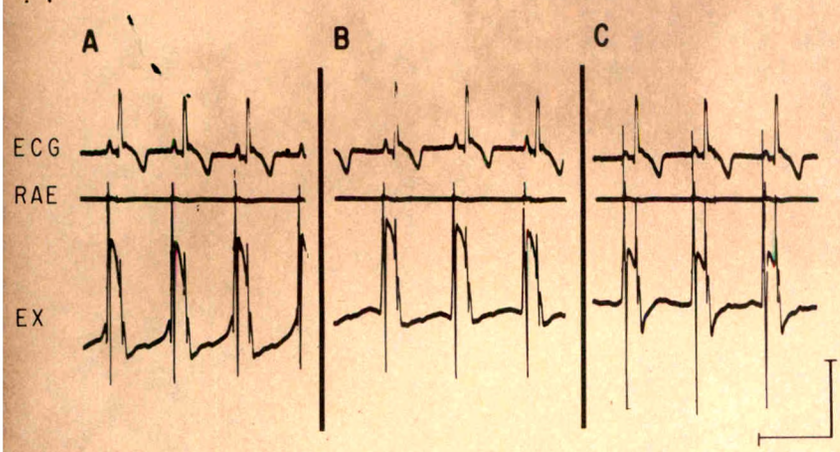


FIGURE 7. Examples of extracell (EX) electrograms obtained near the sinus pacemaker in an in situ heart. **A** is recorded directly over the sinus pacemaker, **B** a few mm anterior on the linea terminalis and **C** a few mm caudal on the atrium. Lead II electrocardiograms (ECG) and right atrial electrograms (RAE) are also shown. The **vertical bar** corresponds to 100 μv on the electrogram and the **horizontal bar** to 100 msec. See text for details.

from isolated canine atrium. The change from diastolic to upstroke slope, representing the onset of sinus nodal depolarization, occurs about 70 msec before the onset of atrial depolarization as measured in the reference atrial electrogram. In the dogs studied with morphine and chloralose anesthesia the sinoatrial conduction time ranged from 40 to 80 msec. We have obtained satisfactory sinus nodal electrograms from the epicardial surface in 31 of the 36 in situ experiments.

Records from another preparation (Fig. 7) show the differences in the sinus nodal electrogram produced by minor changes in the position of the exploring electrode. In each record a surface lead II electrocardiogram and right atrial electrogram are included. In panel A the exploring electrode is located over the primary pacemaking region. Diastolic and upstroke slopes are seen, and the sinoatrial conduction time is approximately 60 msec. Panel B was also recorded from a site on the linea terminalis but about 5 mm anterior to the pacemaking site. This position corresponds to that of point B, Figure 3. Here the sinus electrogram is similar to those recorded from latent pacemaking cells in isolated rabbit or canine preparations. It demonstrates a diastolic slope but does not show an upstroke slope. Panel C is recorded from the atrium about 5 mm caudal to the pacemaking site (position E in Fig. 3). As would be expected, it shows neither a diastolic nor an upstroke slope.

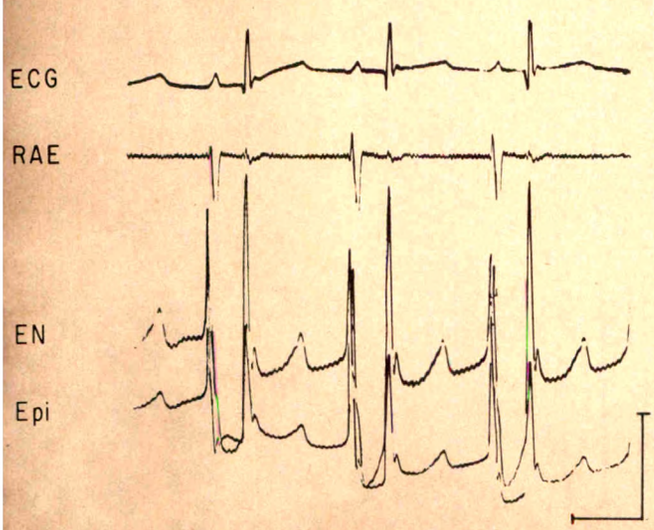


FIGURE 8. Simultaneous sinus nodal electrograms from epicardial (Epi) and endocardial (EN) surfaces. A lead II electrocardiogram (ECG) and right atrial electrogram (RAE) are also shown. The **vertical bar** is 100 μv in the electrogram and the **horizontal bar** is 200 msec. See text for details.

Potentials from the endocardial surface: Because the in vitro experiments had demonstrated that it was possible to record sinus pacemaker potentials from the endocardial surface, we tested the feasibility of recording them from the endocardial surface in situ. Figure 8 shows the results of such an experiment. The primary pacemaking site was localized from the epicardial surface and a no. 4F catheter introduced by way of the right jugular vein and positioned so that the tip rested against the endocardial surface at the same site. Sinus nodal electrograms from both epicardial and endocardial sites are recorded simultaneously. The records are essentially the same, and both demonstrate diastolic and upstroke slopes.

We were able to obtain satisfactory endocardial sinus node electrograms in 19 of 24 animal studies. After the initial experiments confirmed the similarity of epicardial and endocardial records we routinely localized the pacemaker with the catheter before localization from the epicardial surface. We did not attempt localization of the pacemaker in closed chest animals in these studies.

Limitations of the technique: Recording potentials from the sinus node in situ presented several additional problems not seen during the in vitro experiments. First, as the sinus cycle shortens, repolarization potentials from the ventricle overlap the potentials produced by the sinus node. At heart rates in excess of 130 beats/min the T wave produced enough distortion so that it was usually not possible to be certain of the onset of the upstroke slope. Thus, the technique we used is not suitable to study sinus function at rapid heart rates. Second, it was not possible to recognize retrograde depolarization of the sinus pacemaker after an atrial

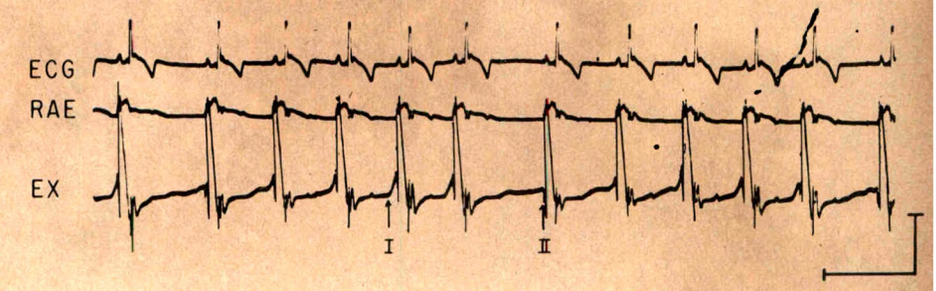


FIGURE 9. Effect of sinus arrhythmia on the sinus nodal electrogram (EX). A lead II electrocardiogram (ECG) and right atrial electrogram (RAE) are also shown. The **first arrow** (I) is during inspiration and the **second** (II) during expiration. The **vertical bar** is 100 μv and the **horizontal bar** 100 msec. See text for details.

premature complex as we had done in the rabbit preparations.[6] In the intact heart the ventricular QRS and T waves produced by anterograde conduction of an atrial premature depolarization occur while the sinus node is being depolarized in a retrograde manner. The larger ventricular potentials modify the baseline of the electrogram so that it is not possible to distinguish the sinus nodal potentials. A final problem is that the primary pacemaking site appears to move much more in situ than it does under controlled conditions in vitro. This is evident particularly at slower heart rates and in the presence of sinus arrhythmia. In Figure 9 the exploring electrode was held in a constant position over one area of the sinus node during sinus arrhythymia. During inspiration, as the heart rate increases the primary pacemaking site is in the immediate vicinity of the electrode (first arrow). Diastolic and upstroke slopes are present in all of these complexes, although sinoatrial conduction time appears to change slightly with each depolarization. Then, as the rate decreases during expiration, the upstroke slope is no longer seen (second arrow). The pacemaking site has moved away from the recording electrode at this time. This pattern is not random and recurs with each respiratory cycle.

Discussion

Characteristics of the canine sinus node: *The canine sinus node* was selected as an experimental model for this study because it closely resembles the human sinus node.[10,11] In both species it is an oval structure located at the junction of the superior vena cava and right atrium and surrounding a prominent sinus nodal artery. It is separated from the epicardial surface by 1 to 2 mm of tissue and from the endocardial surface by 2 to 5 mm of atrial muscle. Microelectrode studies of the canine sinus node are technically difficult because of the distance the microelectrode must travel to impale a pacemaker cell. However, Woods et al.[7] recently demonstrated that its transmembrane action potentials and activation sequence resemble those of the rabbit and other mammals. In all of these species the electrical activity originates in a small region (2 mm^2) within the sinus node and this area is termed the primary pacemaking region. Action potentials from cells in this region show prominent phase 4 depolarization and a smooth transition to phase 0 of the transmembrane action potential. Also, these cells appear to depolarize in unison. Other areas of the sinus node reach threshold later, and the cells usually have less prominent phase 4 depolarization and a more rapid phase 0 upstroke. This study suggests that, despite marked anatomic differences between the rabbit and canine sinus nodes, the extracell potentials produced by each node are similar. To record the onset of sinus node depolarization in either species one must be able to detect a potential produced by cells in the primary pacemaking region and distinguish it from potentials produced in adjacent regions of the node and atrium. An additional problem presented by the canine sinus node is that the pacemaker cells are 1 to 5 mm from the surface.

Characteristic extracell potentials: Our results clearly demonstrate that this distance is not too great and that the pacemaking region of the canine sinus node gives rise to characteristic extracell potentials. These can be recorded from both the endocardial and epicardial surfaces and are recognizable in records from the in situ heart as well as in the case of isolated preparations of sinus node and right atrium. They consist of (1) the diastolic slope, a steady change in potential of −30 to −100 v/sec that occurs as the cells under the electrode are undergoing phase 4 depolarization, and (2) the upstroke slope, another slow potential (−400 to −1,000 v/sec) produced by phase 0 depolarization of sinus pacemaker cells. The change from diastolic to upstroke slope occurs at the same time as pacemaker cells begin phase 0 depolarization and thus serves as a marker of the onset of sinus nodal depolarization. As these studies suggest, these potentials are identical in all respects to those recorded from the rabbit sinus pacemaker.

Relation of extracell and intracell potential: Several lines of evidence support the hypothesis that these extracell potentials are produced by the transmembrane currents of pacemaker cells. First, the complex is recorded only over the pacemaker and shows temporal correlations with phases 4 and 0 of depolarization in records of transmembrane potential. Second, these potentials are similar to extracell complexes we have recorded from the rabbit sinus pacemaker during phase 4 and 0 depolarizations, from Purkinje fibers induced to develop phase 4 depolarizations, and from the canine coronary sinus induced to develop delayed after-depolarizations.[12] In each of these preparations a nonpropagated change in transmembrane potentials is accompanied by an extracell potential that is comparable in size and shape to that recorded from the canine sinus node. Third, the experiments with tetrodotoxin demonstrate that correlation between transmembrane and extracell records of sinus nodal activity are maintained when all other electrical activity is abolished. When electrical activity is limited to the

primary pacemaking region the extracell tracing is a smooth continuous potential similar in shape to but reversed in polarity from the sinus pacemaker transmembrane potential (Fig. 5D).

In situ recordings: Our second major finding is the feasibility of recording these potentials from both the epicardial and endocardial surface of the in situ heart. Recording these small and localized potentials from a vigorously contracting heart requires meticulous attention to be sure that the exploring electrode is positioned exactly over the pacemaking region and maintained in stable contact with the surface of the heart. Although this is sometimes difficult, we found that satisfactory electrograms usually could be obtained with both hand-held probes and catheter electrodes.

Clinical implication: Our study used the canine sinus node because of its resemblance to the human sinus node. We believe that the results suggest that the human sinus node is very likely to produce specific extracell potentials that can be recorded by minor modifications of currently existing techniques. In fact, we have already applied the technique to the recording of sinus nodal electrograms during cardiac catheterization in 26 patients (results to be published).

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Acute Coronary Occlusion in the Pig: Effect of Nitroglycerin on Regional Myocardial Blood Flow

ALBERT S. MOST, MD, FACC
DAVID O. WILLIAMS, MD, FACC
RONALD W. MILLARD, PhD

Providence, Rhode Island

Myocardial blood flow was studied in 10 closed chest, anesthetized pigs after an acute balloon catheter occlusion of the left anterior descending coronary artery. With use of radioactive microspheres (15 μ), myocardial blood flow was measured before and during an intravenous nitroglycerin infusion and during a combined nitroglycerin-phenylephrine infusion. A significant zone of ischemia (myocardial blood flow less than 50 percent of normal zone flow) was produced by the occlusion and involved 15 percent of the combined left ventricular and interventricular septal mass. More than 50 percent of this ischemic zone was intensely ischemic (myocardial blood flow 0 to 3 percent of normal). Nitroglycerin resulted in a 20 to 30 mm Hg decrease in systolic blood pressure. Myocardial blood flow was unchanged in intensely ischemic areas but varied directly with the product of heart rate and systolic blood pressure in the moderately ischemic area (myocardial blood flow 26 to 50 percent of normal). S-T segment elevation was significantly increased during nitroglycerin infusion and returned to control level with the added infusion of phenylephrine sufficient to restore the systemic blood pressure to prenitroglycerin values. No improvement in ischemic zone perfusion could be demonstrated during the infusion of nitroglycerin alone or with phenylephrine. The endocardial/epicardial flow ratio in moderately ischemic areas was slightly lower than the normal zone flow ratio and decreased slightly during infusion of nitroglycerin. With the addition of phenylephrine, the ratios rose slightly and no longer differed from prenitroglycerin values.

Blood flow distribution in acutely ischemic pig myocardium differs considerably from that observed in the dog. Nitroglycerin was not shown to have any beneficial effects with or without its relative hypotensive effect. More extensive study in animal models other than the dog is needed.

Myocardial blood flow after acute coronary occlusion has been studied in detail in the dog, an animal whose heart has an abundant preformed epicardial collateral network.[1–6] The pig heart, in contrast, possesses few collateral vessels, and has been reported to respond to acute coronary occlusion with a greater incidence of myocardial infarction.[7] Importantly, the dog's collateral circulation may also greatly influence the outcome of pharmacologic interventions studied for their effect on tissue survival and vascular adjustments after occlusion. For these reasons we chose to study how an important pharmacologic agent, nitroglycerin, affects myocardial blood flow after an acute coronary occlusion in the pig.

The salutory effect of nitroglycerin in treating angina pectoris is unquestioned and is largely attributed to the peripheral vascular effects of this drug, which result in reduced myocardial oxygen demand.[8] Direct effects of nitroglycerin on the coronary vasculature are less clearly established, but the possibility of a favorable redistribution of blood flow to the more vulnerable ischemic subendocardium has been proposed as an additional beneficial action.[9–11]

From the Division of Cardiology, Department of Medicine, Rhode Island Hospital, Providence, Rhode Island, and the Section of Medicine, Brown University Program in Medicine, Providence, Rhode Island. Manuscript received May 17, 1978; revised manuscript received July 5, 1978, accepted July 5, 1978.

Address for reprints: Albert S. Most, MD, Division of Cardiology, Rhode Island Hospital, Providence, Rhode Island 02902.

Despite numerous investigations in dogs,[11–17] the influence of nitroglycerin on myocardial blood flow after an acute coronary occlusion remains unsettled. Recent work has focused on the use of nitroglycerin, and the effect of vasodilators in general, in acute myocardial infarction in man.[18–22] Patient studies, relying principally on precordial S-T segment mapping, have indicated a potential beneficial effect from nitroglycerin given either intravenously[18,20] or sublingually[19,20,22] in the early stages of an acute myocardial infarction. Microsphere flow studies in dogs suggest that nitroglycerin can enhance subendocardial blood flow to acutely ischemic regions.[11,12,17] Reduction in measured S-T segment elevation further suggests that nitroglycerin may be of benefit.[13–15,17–21,23] However, not all reports indicate that nitroglycerin exerts favorable effects. The "steal" of blood flow by the nonischemic myocardium at the expense of perfusion of ischemic tissue has been proposed as one unfavorable action of nitroglycerin on acutely ischemic dog myocardium.[24] Indeed, Forman et al.[25] found that subendocardial flow in ischemic canine myocardium was reduced after nitroglycerin. In addition, further elevation of S-T segments after occlusion has been reported during nitroglycerin infusion even though ischemic zone flow was unchanged.[16]

This study was undertaken to help define the influence of nitroglycerin on myocardial blood flow in the setting of an acute coronary occlusion in an animal model whose coronary collateral circulation differs considerably from that of the dog. A specific objective was to evaluate the hypothesis that nitroglycerin exerts a salutory action by improving endocardial perfusion of the ischemic regions.

Materials and Methods

Experimental Procedures

Ten farm-bred pigs (25 to 50 kg) were anesthetized with chloralose and urethane and maintained on a positive pressure respirator (Harvard Apparatus, Millis, Massachusetts). With the aid of fluoroscopy, catheters were placed in the aorta, inferior vena cava, left atrium and pulmonary artery through groin and neck incisions. A 15 lead electrocardiographic map was applied to the precordium. Respiration was supported to stabilize arterial pH and maintain arterial partial pressure of oxygen above 90 torr.

Arterial pressure was measured through an aortic catheter attached to a Statham P23Db transducer. Left atrial pressure was monitored in similar fashion. Cardiac output was measured by indocyanine green dye technique (Lexington Instruments Corp., Waltham, Massachusetts) with pulmonary arterial injections and aortic sampling. Duplicate output determinations, agreeing within 10 percent, were averaged for a single result. Heart rate was derived from the electrocardiogram and the product of heart rate and systolic arterial pressure calculated (double product).

Microspheres (diameter 15 ± 3 μ [standard error of the mean]) labeled with scandium-46, strontium-85, cerium-141 or chromium-51 were suspended in 10 percent dextran-0.01 percent Tween 80® solution to a final approximate concentration of 4×10^6 microspheres/ml. The suspension was sonically disrupted for 15 minutes with an ultrasonic probe (Heat Systems Ultrasonics, Inc., Rochester, New York) and dispersion microscopically verified just before injection. Approximately 4×10^6 spheres were injected for each flow determination. Injections over 5 to 10 seconds into the left atrium were immediately followed by a rapid 10 ml normal saline flush. An organ reference sample was drawn from the aortic catheter over 2 minutes beginning 15 seconds before the microsphere injection. The withdrawal rate was 15 ml/min.

Protocol

The precordial electrocardiographic map was recorded (paper speed 25 mm/sec, 1 mv = 20 mm) simultaneously with left atrial and arterial blood pressure after cardiac output measurement. This completed a control state. Coronary occlusion was next carried out. Under fluoroscopic guidance, a shortened no. 8F thin-walled Cournand catheter was passed into the left anterior descending coronary artery. A small injection of contrast material (Renografin-76®, E. R. Squibb & Sons, Inc., New Brunswick, New Jersey) confirmed this position. A no. 3F balloon-tipped embolectomy catheter was then passed through the larger catheter into the left anterior descending artery. The larger catheter was withdrawn into the aorta. "Inflation" of the balloon catheter in the mid left anterior descending artery was accomplished by distending the balloon with liquid mercury under fluoroscopic observation. A closed stopcock sealed the balloon catheter, preventing deflation of the balloon. An electrocardiographic map and hemodynamic variables were recorded 45 minutes after occlusion. At this point a microsphere injection was made. Nitroglycerin (300 μg/ml) (supplied in liquid form by Eli Lilly Co., Indianapolis, Indiana) was then infused intravenously at a rate sufficient to decrease arterial systolic pressure 20 to 30 mm Hg (6 to 38 μg/kg per min). Once this was achieved for 5 to 10 minutes, all measurements were repeated including a second microsphere injection. Phenylephrine (200 μg/ml) was then infused intravenously (0.02 to 1.0 μg/kg per min), as nitroglycerin infusion continued, to restore the systolic arterial pressure to the value that preceded the nitroglycerin infusion. All measurements, including the third microsphere injection, were repeated. The animal was then killed with an overdose of intravenous potassium chloride.

The entire heart was sectioned for differential gamma spectrometry. The interventricular septum was separated from the free left ventricular wall. Septal pieces were divided into right and left halves. Left ventricular sections were divided into endocardial and epicardial halves. Final sections ranged in weight from 0.3 to 1.2 g with the smaller sections concentrated in the area of the infarction. The right ventricle and atria were not considered in this analysis. Each myocardial tissue sample containing three groups of differently labeled microspheres was subjected to counting in a gamma well counter (Packard Instruments Company, Inc., Downers Grove, Illinois). Differential spectrometric data from the gamma counter were printed on teletype link and simultaneously punched on paper tape. The tape, with ancillary information of tissue weights, reference arterial blood volume, time and radioactive count totals, was applied to a digital computer (PDP-11/40, Digital Equipment Corp., Maynard, Massachusetts). Simultaneous solutions of equations for three unknowns were performed to yield blood flow per unit weight for each sample. Program subroutines allowed assemblage of epicardial and endocardial samples by flow ranges normalized to the nonischemic regions.

Data Analysis

Precordial S-T segment map: S-T segment voltage elevation was measured 0.10 second after the beginning of the QRS complex using the P-R segment voltage as the reference level. Only leads with a positive S-T segment throughout were included in each animal's S-T segment data. The individual S-T values were averaged for a mean S-T value.

TABLE I

Weight Distribution of Ischemic Myocardium After Acute Coronary Occlusion in the Pig (mean ± standard error of the mean)

Myocardial Blood Flow (% of normal zone flow)	Endocardium (g)	Epicardium (g)	% of Total Left Ventricle*
0–10	2.52 ± 0.52 (10)	3.48 ± 0.57 (10)	8.65 ± 1.47
11–25	1.34 ± 0.26 (9)	1.28 ± 0.30 (9)	3.40 ± 0.74
26–50	1.31 ± 0.22 (10)	1.79 ± 0.35 (9)	4.34 ± 0.63

* Combined endocardial and epicardial weights.
Figures in parentheses indicate the number of animals with tissue sections in a specific flow category.

TABLE II

Hemodynamics Before and After Acute Coronary Occlusion in the Pig: Effects of Nitroglycerin and Nitroglycerin Plus Phenylephrine After Occlusion (mean ± standard error of the mean)

	Control (preocclusion)	Pre-NTG	NTG	NTG/PE
Heart rate (beats/min)	128 ± 12	127 ± 11	152 ± 11*	117 ± 14†
Arterial pressure (mm Hg)				
Systolic	155 ± 5	142 ± 5	117 ± 5*	147 ± 5†
Diastolic	116 ± 5	107 ± 3	86 ± 5*	98 ± 5†
Mean	133 ± 6	122 ± 4	98 ± 5*	126 ± 4†
Left atrial pressure (mm Hg)	7.1 ± 1.4	7.5 ± 1.4	5.1 ± 0.9*	7.1 ± 1.2†
Cardiac output (liters/min)	3.5 ± 0.4	2.8 ± 0.3	2.5 ± 0.3	2.5 ± 0.2
Heart rate × systolic pressure × 10^{-3} (double product)	20.1 ± 2.3	18.3 ± 1.9	18.0 ± 1.8	17.4 ± 2.3

* Significant difference (probability [P] < 0.05) between pre-NTG and NTG values.
† Significant difference (P <0.05) between NTG and NTG/PE values.
NTG = nitroglycerin; PE = phenylephrine.

Myocardial blood flow: A "normal zone" of left ventricle was defined as a region anatomically remote from the area of ischemia with relatively homogeneous flow. Seven to 12 paired endocardial-epicardial tissue sections from an area so identified were reassembled by a computer as a hypothetical single piece of tissue that yielded normal values for endocardial, epicardial and transmural blood flow. Using normal zone endocardial and epicardial flow values before the drug intervention as a reference, left ventricular and septal tissue sections were identified in the distribution of the left anterior descending coronary artery in which blood flow was 0 to 10, 11 to 25 and 26 to 50 percent of normal zone flow. Left ventricular septal sections were treated as left ventricular endocardium and right ventricular septal sections as left ventricular epicardium, but these sections were not included in the analysis of endocardial/epicardial flow ratios.

Endocardial/epicardial flow ratios in ischemic zones were derived using two different methods for selected segments of left ventricular free wall. First, ventricular transmural tissue segments were reassembled by combining ischemic endocardial sections (flow 26 to 50 percent of normal zone endocardial flow) with their overlying epicardial section. In animals with more than one such segment total flow was divided by total weight to give a true composite flow. The endocardial/epicardial ratio was calculated for each of the three flow determinations. Second, left ventricular transmural tissue segments were selected in which transmural flow was 20 to 60 percent of normal zone transmural flow. This expanded flow range enabled the second analysis to encompass the same population of animals as the first analysis. Composite areas were reassembled as before and flow was analyzed in terms of transmural, endocardial and epicardial flows, including the ratio of endocardial to epicardial flow.

Statistics: Data were analyzed using Student's t test for groups and the paired t test when changes within groups were examined. A probability (P) value of <0.05 was considered the lower level of significance. Regression analysis was carried out on an Olivetti 101 calculator. Once again a P value <0.05 was necessary to consider a correlation significantly different from zero.

Results

Profile of ischemia: The profile of myocardial blood flow distribution 45 minutes after occlusion is shown in Table I. Of the total left ventricular plus septal mass of 69 ± 3 g (mean ± standard error of the mean) (no. = 10), nearly 15 percent had a blood flow less than 50 percent of normal zone flow. More than half of this flow zone was severly ischemic, with flows 0 to 3 percent of those in the normal zone.

Hemodynamics: Hemodynamics before and after coronary occlusion are shown in Table II. After coronary occlusion no significant changes occurred in arterial pressure, left atrial pressure or cardiac output. Nitroglycerin reduced arterial systolic pressure by the desired amount (20 to 30 mm Hg). Heart rate increased significantly during nitroglycerin infusion; however, the double product of heart rate and pressure did not change. Left atrial pressure decreased and cardiac output was slightly reduced. As arterial pressure was restored by phenylephrine, a concomitant decrease in heart rate resulted, with no change in double product. Left atrial pressure rose to prenitroglycerin levels and cardiac output was unaffected.

Myocardial blood flow: When mean values for myocardial blood flow were considered, the only significant change was an increase in endocardial flow (P <0.05) in the normal zone when phenylephrine restored the blood pressure to prenitroglycerin levels (Table III). Comparisons were made between each successive condition as well as between the first (prenitroglycerin) and

TABLE III

Endocardial and Epicardial Flows (ml/100 g per min) in Normal and Ischemic Zones of Myocardium Before and After Drug Infusions After Acute Coronary Occlusion (mean ± standard error of the mean)

Zone (no. endo/no. epi)	Endocardial Flow			Epicardial Flow		
	Pre-NTG	NTG	NTG/PE	Pre-NTG	NTG	NTG/PE
Normal (10/10)	156 ± 14	145 ± 21	172 ± 26*	140 ± 15	136 ± 19	154 ± 24
Ischemic (% of normal)						
0–10% (10/10)	3 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1	2 ± 1
11–25% (9/9)	26 ± 3	22 ± 5	29 ± 6	24 ± 3	23 ± 3	25 ± 4
26–50% (10/9)	60 ± 5	59 ± 7	69 ± 11	53 ± 7	60 ± 13	62 ± 11

* = Significant difference (probability [P] <0.05) between NTG and NTG/PE values.
endo = endocardium; epi = epicardium; no. = number of animals with tissue sections in a specific flow category; NTG = nitroglycerin; PE = phenylephrine.

final condition (nitroglycerin/phenylephrine). Although, with that one exception, mean values were unchanged, individual pigs experienced considerable flow change. For example, in the normal zone endocardium, with the infusion of nitroglycerin, flow decreased in six (16 to 54 percent), was unchanged in two (± 2 percent) and increased in two pigs (35 and 37 percent). The addition of phenylephrine was associated with an increase in endocardial flow in 8 of 10 pigs. Both normal and moderately ischemic zone (26 to 50 percent of normal zone flow) endocardial blood flows were significantly correlated with double product in each condition studied (Table IV). To determine if flow in the moderately ischemic zone was responsive to alterations in myocardial metabolic demand, the percent change of myocardial blood flow and of double product were correlated (Fig. 1). A significant positive correlation existed for both the nitroglycerin change alone and the combined nitroglycerin and nitroglycerin/phenylephrine data (Fig. 1).

The endocardial/epicardial flow ratio in the normal zone decreased slightly with nitroglycerin and returned to the control level with the addition of phenylephrine (Table V). In sections with transmural flow 20 to 60 percent of normal zone transmural flow, the endocardial/epicardial flow ratio was similar to that in the normal zone, decreased significantly with nitroglycerin and was again not significantly different compared with either prior value after the addition of phenylephrine. In recreated transmural sections of tissue selected for endocardial flow 26 to 50 percent of normal zone en-

TABLE IV

Correlation of Normal and Ischemic Endocardial Flows With Systolic Pressure × Heart Rate Product

Endocardial Flow Zone	no.	Correlation Coefficient		
		Pre-NTG	NTG	NTG/PE
Normal	10	0.6436	0.8863	0.7568
P value		<0.05	<0.001	<0.05
Ischemic (26–50%)	10	0.6581	0.9266	0.8640
P value		<0.05	<0.001	<0.01

Abbreviations as in Table II.

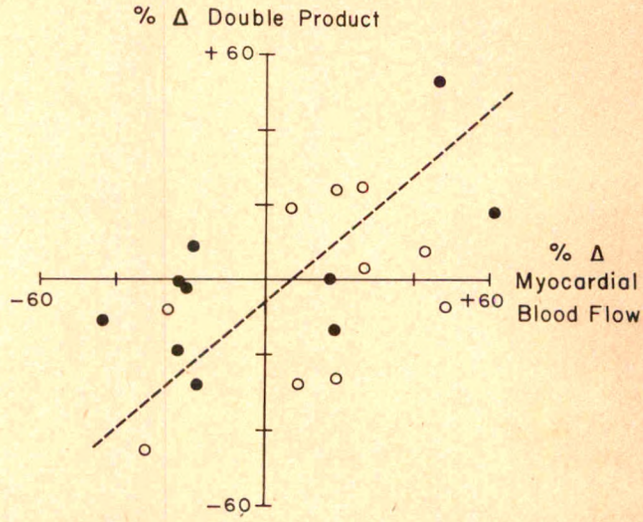


FIGURE 1. Correlation of percent change (% Δ) in double product (arterial systolic pressure × heart rate) with percent change in ischemic endocardial blood flow (26 to 50 percent of normal zone endocardial flow) during nitroglycerin (●) and combined nitroglycerin/phenylephrine (○) infusion ($r = 0.5363$, $P < 0.05$).

TABLE V

Endocardial/Epicardial Flow Ratios for the Normal Zone, a Zone With Transmural Ischemia and a Zone With Endocardial Ischemia

Zone	Pre-NTG	NTG	NTG/PE
Normal (10)	1.13 ± 0.04	1.07 ± 0.05*	1.11 ± 0.03
Transmural ischemia (9)*	1.23 ± 0.16	1.00 ± 0.12*	1.04 ± 0.12
Endocardial ischemia (9)*	0.97 ± 0.15	0.85 ± 0.14*	0.90 ± 0.13

* Transmural ischemia = transmural flow 20 to 60 percent of normal zone transmural flow; endocardial ischemia = transmural zone with endocardial flow 26 to 50 percent of normal zone endocardial flow.
Numbers in parentheses indicate the number of animals with tissue sections in that flow range.
Abbreviations as in Table II.

docardial flow, the endocardial/epicardial ratio of flow before nitroglycerin was 0.97 + 0.15. Nitroglycerin significantly reduced this ratio to 0.85 ± 0.14 ($P < 0.05$) and phenylephrine restored the ratio to 0.90 + 0.13, a value not different from the prenitroglycerin value. The decrease in the ratio after nitroglycerin was not accompanied by a significant change in either endocardial or epicardial blood flow in any of these specially defined zones.

S-T segment mapping: S-T voltage increased significantly with infusion of nitroglycerin and decreased with the addition of phenylephrine (Fig. 2). When compared with values in a group of similar pigs with infarction that received no drug infusions,[26] the preinfusion mean S-T value was very close to the mean S-T time-regression line for those control animals. Instead of decreasing as it did in the control animals in the subsequent time period, a significant increase of mean S-T occurred during nitroglycerin infusion. Combined nitroglycerin-phenylephrine infusion returned the mean S-T value to the control group's regression line.

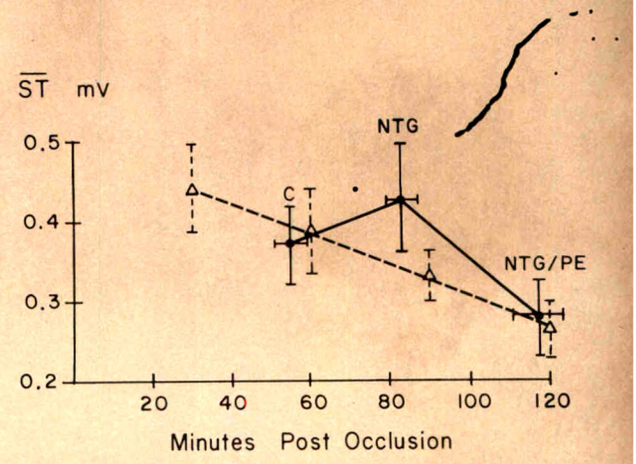


FIGURE 2. Time course of S-T segment changes after acute coronary occlusion in the pig. Values before (C) and during nitroglycerin (NTG) and combined nitroglycerin/phenylephrine (NTG/PE) infusion are shown with a **solid line** (no. = 9). These data are compared with those from a group of animals (no. = 8) with similar coronary occlusion that received no infusions (**broken line**). Data shown are mean ± standard error of mean.

Discussion

Myocardial blood flow after acute coronary occlusion has been studied extensively in the dog, an animal with a well developed epicardial collateral network. Although many patients with ischemic heart disease also have a significant collateral network, this circulation is *developed* in response to ischemia and is largely subendocardial in location.[7] The degree of development of this adaptive network is time-dependent and consequently is not uniformly present when abrupt coronary occlusion develops in man.[27,28] The pig heart, lacking appreciable preformed collateral vessels,[7] but possessing an anastomotic network in the subendocardium similar to that described in normal man,[29] permits the study of changes in ischemic zone blood flow after abrupt coronary occlusion as they may occur in a significant subset of patients.

Ischemic zone myocardial flow in pig, dog and baboon: Our investigation demonstrated that, in the pig, the myocardial infarct zone contains a core of severely ischemic muscle that may not be amenable to pharmacologic influence. Fully 56 percent of the ischemic zone (0 to 50 percent of normal zone flow) was severely ischemic with flow only 0 to 3 percent of that in the normal zone. This core of intense ischemia contrasts with the core ischemic flow in dogs, which is significantly greater (15 to 50 percent of control) and less uniform.[1,2,4–6]

The pig appears to resemble the baboon closely in terms of acute postocclusion flows. Core ischemia is quite intense in the baboon[30,31] with flows consistently below 15 percent of preocclusion levels.[30] In addition, endocardial flow is equal to or exceeds epicardial flow in tissue just within the "inner border of the visual edge" of the baboon infarct. This area in the baboon corresponds to the moderately ischemic zone in the pig where the endocardial/epicardial flow ratio similarly was not reduced. The latter observation is in contrast to results in the dog.[1–3] Intense core ischemia and no reduction in the endocardial/epicardial flow ratio in the infarct margins are therefore features common to both the pig and baboon.

Relation of endocardial flow and double product: Normal zone endocardial flow was correlated in a positive manner with "double product" of heart rate and blood pressure in each of the three conditions studied. This relation is consistent with the concept that myocardial oxygen demand is the major determinant of myocardial blood flow.[32] Although *changes* in double product and flow were not significantly correlated for normal endocardium, as was seen in the ischemic myocardium, there was a similar trend toward positive correlation, which suggests that normal endocardial flow did respond appropriately to measured demand factors. Changes in contractility, also contributing to normal zone oxygen demand, may account for the failure of changes in double product to correlate significantly with changes in normal endocardial flow.

The significant relation between ischemic endocardial flow and double product is more difficult to understand. Flow that is 26 to 50 percent of normal is associated with a considerable impairment of contractile function.[33] Double product, a demand factor, still appears to be a significant determinant of flow in the ischemic region where vasodilatory reserve is presumably exhausted. One possible explanation is that flow to ischemic tissue first passes through adjacent normal tissue where arteriolar sphincters are still responsive to the demand factors. This communication at the postarteriolar level may be the type of anastomosis that exists, as previously noted,[29] in the subendocardium. Such an anastomosis could account for a margin of low flow tissue where flow could be responsive to the same factors influencing normal zone flow. A second possibility is that the marginally ischemic region is an admixture of both normally perfused and severely underperfused tissue at the infarct rim.[34]

Recent work by Cohen[34] has helped define the relative contributions of overlap flow and true collateral blood flow to the perfusion of ischemic regions in the

dog heart. In a partially perfused dog heart, both artifactual overlap (sectioning technique) and true anatomic overlap were found to account for half of ischemic tissue flow whereas true collateral flow accounted for the other half.

Effect of nitroglycerin on ischemic myocardial flow: The infusion of nitroglycerin, by reducing arterial pressure and decreasing diastolic filling time, might have been expected to result in diminished perfusion of ischemic myocardium where maximal vasodilatation would limit the capacity for further autoregulation. Such was not the case when total flow was considered. This finding is in accord with the previously advanced hypothesis that changes in ischemic zone flow are closely tied to flow adjustments in the normally perfused adjacent tissue.

The endocardial/epicardial flow ratio decreased slightly in both normal and ischemic zones during nitroglycerin infusion, although actual flows were unchanged in both the endocardium and the epicardium. Phenylephrine restored these ratios to values not significantly different from prenitroglycerin levels, suggesting that the slight shift in transmural flow may have been due to the systemic hemodynamic effect of nitroglycerin and not to a specific effect on coronary vasculature. The minimal nature of these changes in flow was in contrast to the very substantial changes in arterial blood pressure induced by nitroglycerin. Recent canine studies on the effect of nitroglycerin on myocardial blood flow after acute coronary occlusion report encouraging effects in terms of improved ischemic zone flow.[11,12,17] Although these studies disagree in a number of aspects, it appears that the pig's postocclusion myocardial blood flow pattern is influenced far less by systematically infused nitroglycerin, with or without an alpha adrenergic agonist.

The possibility of alpha adrenergic coronary vasoconstriction offsetting improved perfusion factors under the influence of phenylephrine deserves consideration. Norepinephrine can cause coronary vasoconstriction, even in the face of increased oxygen demand attributed to this drug.[35] Autoregulation in response to metabolic demand can seemingly be overridden under selected circumstances.[36] However, the influence of alpha adrenergic coronary constriction in the setting of an acute coronary occlusion has not been studied.

The possibility of a "coronary steal,"[24] with nitroglycerin vasodilating the vascularity of normal myocardium to the detriment of ischemic myocardium with a fully dilated vascular bed, gains little support from our data. Normal and ischemic zone flow during nitroglycerin infusion did not vary in a manner to indicate preservation of normal zone flow at the expense of ischemic zone flow. In addition, the transmural distribution of myocardial blood flow was similarly affected by nitroglycerin in both normal and ischemic regions.

S-T elevation during nitroglycerin infusion: Considering the modest hemodynamic effects of the drug infusions, why did S-T elevation increase during nitroglycerin infusion and decrease with the addition of phenylephrine? The modest tachycardia and relative hypotension secondary to nitroglycerin could possibly have intensified ischemia and account for the heightened S-T segments seen after nitroglycerin.[23] However, ischemic endocardial flow did appear to adjust to changes in double product of heart rate and blood pressure, and actual flow changes did not suggest intensified ischemia. Becker[16] observed a similar increase in S-T segment elevation with the infusion of nitroglycerin after coronary occlusion in dogs. This was reversed by the addition of methoxamine, which restored blood pressure to the prenitroglycerin level. Myers et al.[15] similarly found the combination of nitroglycerin and methoxamine to reduce ischemic injury as measured by S-T segment changes. In our study the addition of phenylephrine to restore blood pressure had no net favorable influence on S-T segments but did blunt the S-T elevation seen during nitroglycerin infusion. Furthermore, the tachycardia consequent to the nitroglycerin infusion was mild and in the range (20 percent) reported by Becker[37] to have no significant effect on ischemic zone blood flow in dogs.

Caution regarding the interpretation of S-T segment change as a specific indicator of severity of ischemia is suggested by the observations that: (1) epicardial S-T segment changes correlate poorly with degree of myocardial ischemia[38,39] as well as with myocardial creatine kinase 24 hours after coronary occlusion in dogs[39]; (2) a prompt decline in S-T segment elevation follows reperfusion of ischemic myocardium in the pig in the face of subsequent massive intramyocardial hemorrhage[40]; and (3) differences in regional contractility can produce S-T segment changes independent of variations in the degree of ischemia.[41]

Clinical implications: The administration of nitroglycerin in this study to pigs with normal left atrial pressure may not have the same influence on myocardial blood flow as administration of this drug in the presence of high filling pressures because an elevated filling pressure has been shown to impair ischemic endocardial blood flow in the dog.[10] Therefore, caution must be exercised in extrapolating data from these experiments to the clinical setting where filling pressures are often significantly elevated.

Interspecies differences in animal infarct models deserve careful attention. The canine infarct zone is far better perfused than the porcine infarct zone. Better penetration of pharmacologic agents would be anticipated and could possibly have a more significant impact on the natural history of the ischemic zone. Neither animal model fully satisfies the human condition, and optimistic conclusions based on canine studies may be falsely encouraging, whereas pessimistic reports, based on porcine studies, may be unnecessarily discouraging. Both models may represent extreme positions. Neither approaches the ideal condition in which progressive coronary lesions lead to acquired collateralization that in part ameliorates the effect of an abrupt decrease in myocardial perfusion.

Acknowledgment

We gratefully acknowledge the technical assistance of Thomas DeVona, Larry Grimaldi, Lorraine Schofield and Luis Sousa and the secretarial assistance of Christine Abatiello and Carol White.

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Two and Three Dimensional Display of Myocardial Ischemic "Border Zone" in Dogs

ALDEN H. HARKEN, MD, FACC
CLYDE H. BARLOW, PhD
WESLEY R. HARDEN, III, MD
BRITTON CHANCE, PhD

Philadelphia, Pennsylvania

It is intuitively apparent that the ultimate fate of reversibly damaged, peri-ischemic "border zone" tissue should relate to individual patient survival. The purpose of this study was: (1) to describe a technique of assessing the adequacy of epicardial and myocardial oxygenation, and (2) to examine the extent and character of the peri-ischemic "border zone" in the dog after coronary arterial ligation. A diagonal branch of the left anterior descending coronary artery was ligated in four anesthetized open chest, neurohormonally intact dogs. The same diagonal coronary artery was ligated in six isolated perfused canine heart preparations in which coronary partial pressures of oxygen and carbon dioxide, pH, blood flow and temperature were fixed. The ischemic zones were rapidly frozen and reduced nicotinamide adenine dinucleotide (NADH) fluorescence photographs were taken of the epicardium and at 0.5 mm depths into the myocardium. The distinction between perfused and ischemic myocardium is not apparent with the naked eye or natural light photography. Epicardial and myocardial oxidation-reduction status is well seen with NADH fluorophotography. In both the intact and perfused heart preparations the NADH-fluorescent (ischemic) border is jagged along all edges. Islands of perfused nonfluorescent tissue appear within the ischemic border. The transition between NADH-fluorescent ischemic cells and adjacent nonfluorescent tissue is less than 0.1 mm. The ischemic border is narrow. The distance between homogeneously NADH-fluorescent tissue and homogeneously nonfluorescent tissue (across the zone of island normoxia or microheterogeneity) may be as wide as 6 to 8 mm.

Abrupt coronary arterial occlusion in the experimental animal leads to regional hypoperfusion and local tissue hypoxia. Human coronary insufficiency is probably a less abrupt phenomenon and the degree of overlap between experimental and clinical myocardial ischemia is not clear. However, after 10 to 15 seconds of experimental myocardial hypoxia, TQ-ST segment changes occur[1] and contractility decreases.[2] The concurrent shift from aerobic and anaerobic metabolism permits analysis with direct tissue biopsy[3] or indirect venous efflux metabolite collection.[4,5] The spatial resolution of the biopsy technique has been limited by the size of the biopsy drill (usually 3 or 4 mm in diameter). Recently, the character and extent of the ischemic zone and the peri-ischemic border zone have been further examined in dogs.[6] The existence of a border zone of intermediate tissue injury has great clinical relevance and is currently being questioned.

A precise reflection of regional myocardial oxygen supply and demand ratio should permit better delineation of myocardial ischemia and justify further investigation into its pharmacologic and surgical modification. The purpose of this manuscript is (1) to describe a technique for assessing the adequacy of epicardial and myocardial oxygenation, and (2) to examine the extent and character of the peri-ischemic "border zone" in the dog after coronary arterial ligation.

From the Department of Cardiovascular Surgery and the Johnson Foundation, University of Pennsylvania Medical School, Philadelphia, Pennsylvania. This study was supported in part by Grant 1 RO1 HL-22315-01 from the National Institutes of Health, Bethesda, Maryland. Manuscript received May 9, 1978; revised manuscript received July 5, 1978, accepted July 5, 1978.

Address for reprints: Alden H. Harken, MD, Department of Cardiovascular Surgery, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

Methods

Myocardial ischemia in anesthetized open chest preparation: Four male mongrel dogs, 20 to 28 kg, were anesthetized with sodium pentobarbital, 25 mg/kg body weight. Systemic blood pressure was monitored with a femoral arterial cannula and continuously displayed on a multichannel recorder (Electronics for Medicine model GR 9). The animals were intubated and ventilated (12 ml/kg tidal volume) to maintain normal acid-base status. The heart was approached through a left thoracotomy. A diagonal branch of the left anterior descending coronary artery was ligated to produce a small zone of ischemia on the left ventricular free wall. The ischemic insult persisted for 5 minutes. Large Wollenberger tongs[7] (8 by 8 cm) were cooled in liquid nitrogen and abruptly placed across the ischemic zone so that this area was in the center of the large cold metal plate. The frozen portion of the heart was rapidly amputated and the tongs plus attached left ventricle were plunged immediately into liquid nitrogen.

Myocardial ischemia in isolated perfused heart preparation: Six mongrel dogs, 19 to 22 kg, of both sexes were anesthetized with sodium pentobarbital, 25 mg/kg. The heart was approached through a right thoracotomy. The innominate artery and right atrium were cannulated for a period of blood and temperature equilibration on partial cardiopulmonary bypass. An isolated, perfused decompressed heart (Fig. 1) was prepared by ligating the superior and inferior venae cavae and cross-clamping the transverse aortic arch.[8] A thermistor probe was placed through a purse string suture in the right atrium for temperature measurement. A membrane-lung perfusion system[8,9] permitted fixed coronary blood flow, stable coronary arterial partial pressures of oxygen and carbon dioxide and pH, and constant blood temperature.

A left thoracotomy revealed the left ventricle. After a 30 minute period of stabilization, a diagonal branch of the left anterior descending coronary artery was ligated. The ischemic insult persisted for 5 minutes. Large Wollenberger tongs[7] were placed across the left ventricle and the heart was rapidly frozen as previously described.

NADH fluorescence photography of frozen ischemic zones: The quick-frozen left ventricular epicardium and myocardium were then shaved or filed off in successive measured layers. The shaving blade and file were precooled in liquid nitrogen.

Nicotinamide adenine dinucleotide (NADH) fluorescence photographs were taken of the epicardial and myocardial surfaces at each level. This photographic technique has previously been described in reports from this laboratory.[10,11] NADH fluorescence photographs were taken with a Bronica S2A camera. Corning 9788 and Wratten 45 filters were placed over the camera lens to allow transmission of NADH fluorescence in the 430 to 510 nanometer (nm) region. NADH fluorescence excitation was provided by two 400 joule xenon flashtubes (EG and G FX-47C3) covered by Corning 5840 filters to provide 330 to 380 nm excitation.

Results

Anesthetized open chest animals: Mean systemic blood pressure before coronary arterial ligation was 115 ± 10 torr (standard error of the mean) and 5 minutes after ligation was 105 ± 9 torr. Heart rate was 120 ± 8 before and 126 ± 6 beats/min after ligation. Arterial oxygen tension (PO_2) was 85 ± 10 torr before and 84 ± 11 after occlusion. Arterial pH was 7.48 ± 0.02 with arterial PCO_2 of 32 ± 5 torr before and pH 7.47 ± 0.015 with arterial PCO_2 of 30 ± 6 torr after occlusion. Conditions before and after arterial ligation were not different.

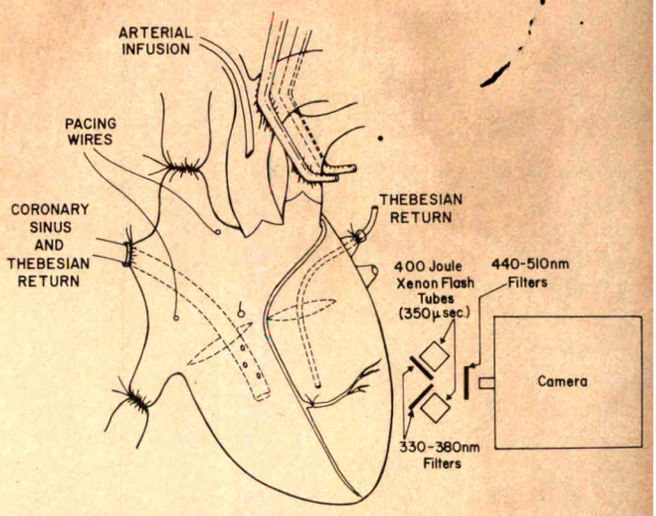


FIGURE 1. Isolated beating heart doing no external pressure or flow work. Arterial blood is infused by way of the innominate artery, courses retrograde down the ascending aorta and out the coronary arteries. Venous blood is collected from the left-sided Thebesian system and the coronary sinus and Thebesian systems on the right. Catheter decompression of both ventricles prevents any external pressure or flow work. Fluorescence photographic instrumentation: A 350 μsec flash from two 400 joule xenon flash tubes is directed at the left ventricle and filtered through 330 to 380 nm filters. Emitted fluorescence, designating reduced NADH, is filtered at 440 to 510 nm and a photograph taken. This technique permits delineation of the oxygen supply/demand ratio over the entire surface of the epicardium or frozen myocardial specimen.

Isolated perfused heart preparation: In each perfused heart, coronary blood flow (pump flow) was regulated to produce a mean aortic (coronary ostial) pressure of 100 torr. This flow was absolutely fixed in each animal between 150 and 200 ml/min. Before and after coronary ligation, coronary blood flow did not change. There was no recognizable change in mean aortic pressure (100 ± 2 torr) associated with coronary occlusion. Coronary arterial PO_2 was 85 ± 9 torr, PCO_2 was 38 ± 2 torr and pH was 7.41 ± 0.015. Coronary arterial oxygen and acid-base status did not change with ligation of the diagonal coronary artery. Right atrial blood temperature remained 37 ± 0.2° C during coronary occlusion.

NADH fluorescence photographs: After rapid freezing of each heart, NADH fluorescence photographs were taken of the epicardial ischemic zone and at sequential levels down into the ischemic myocardium. Figure 2A is a natural white light photograph of an intramyocardial ischemic zone from a working heart. The epicardium has been shaved off to a depth of 1.5 mm. The distinction between perfused and ischemic myocardium is not well seen. Figure 2B is an NADH fluorescence photograph of the identical rapid-frozen intramyocardial ischemic zone. The course of the coronary artery, the level of the ligature and the hematoma are as noted. The distinction between the bright NADH fluorescence in the ischemic area and the nonfluorescent normoxic zone is evident.

NADH fluorescence photographs of a rapid-frozen isolated decompressed heart 5 minutes after ligation of a diagonal branch of the left anterior descending coronary artery are depicted in Figure 3. The outer 0.5 mm (Fig. 3A), 1.0 mm (Fig. 3B) and 1.5 mm (Fig. 3C) of epicardium has been shaved off. Fat and collagen fluoresce brightly. A peninsula of NADH fluorescence surrounds the ligated coronary artery distal to the occlusion. The NADH-fluorescent ("ischemic") border is jagged along all edges. Within the ischemic area the NADH fluorescence is not homogeneous. Islands of nonfluorescent tissue appear within the ischemic border. An enlarged photograph (Fig. 3D) of the heterogeneous fluorescence at the ischemic border reveals a central fluorescent core in many of the islands of normoxic tissue (also seen in Fig. 2B).

NADH fluorescence photographs of a rapid-frozen working heart 5 minutes after ligation of a diagonal branch of the left anterior descending coronary artery were examined. Again, the junction between NADH-fluorescent and nonfluorescent zones was jagged. Islands of nonfluorescent tissue within the ischemic border created a zone of microheterogeneity.

The junction at the jagged border of fluorescent tissue and the edge of each nonfluorescent (normoxic) island is always abrupt. Gradations in intensity of NADH fluorescence are not seen. The distance between complete NADH fluorescence and complete nonfluorescence is in every instance less than the spatial resolution of this technique (less than 0.1 mm).

Discussion

Experimental myocardial ischemic tissue has been distinguished from adjacent normally perfused tissue with a variety of methods.[2–6] In each instance, the capability of discerning regional heterogeneity is limited by the spatial resolution of each technique. The transition zone separating the core of an ischemic area from the surrounding normal tissue has traditionally been described as a critical "border zone" of reversibly damaged or jeopardized tissue.[12] If this zone of reversibly damaged tissue is large, it is intuitively apparent that its fate should ultimately relate to individual patient survival.[13] The converse may also be true.

During the past 2 decades, evidence has accumulated to suggest a narrow transition between normal and ischemic myocardium. Caulfield and Klionsky[14] found a distance of 0.1 mm between pathologically normal and damaged myocardium. Fischl et al.[15] found blood flow in the central and lateral portions of an ischemic area

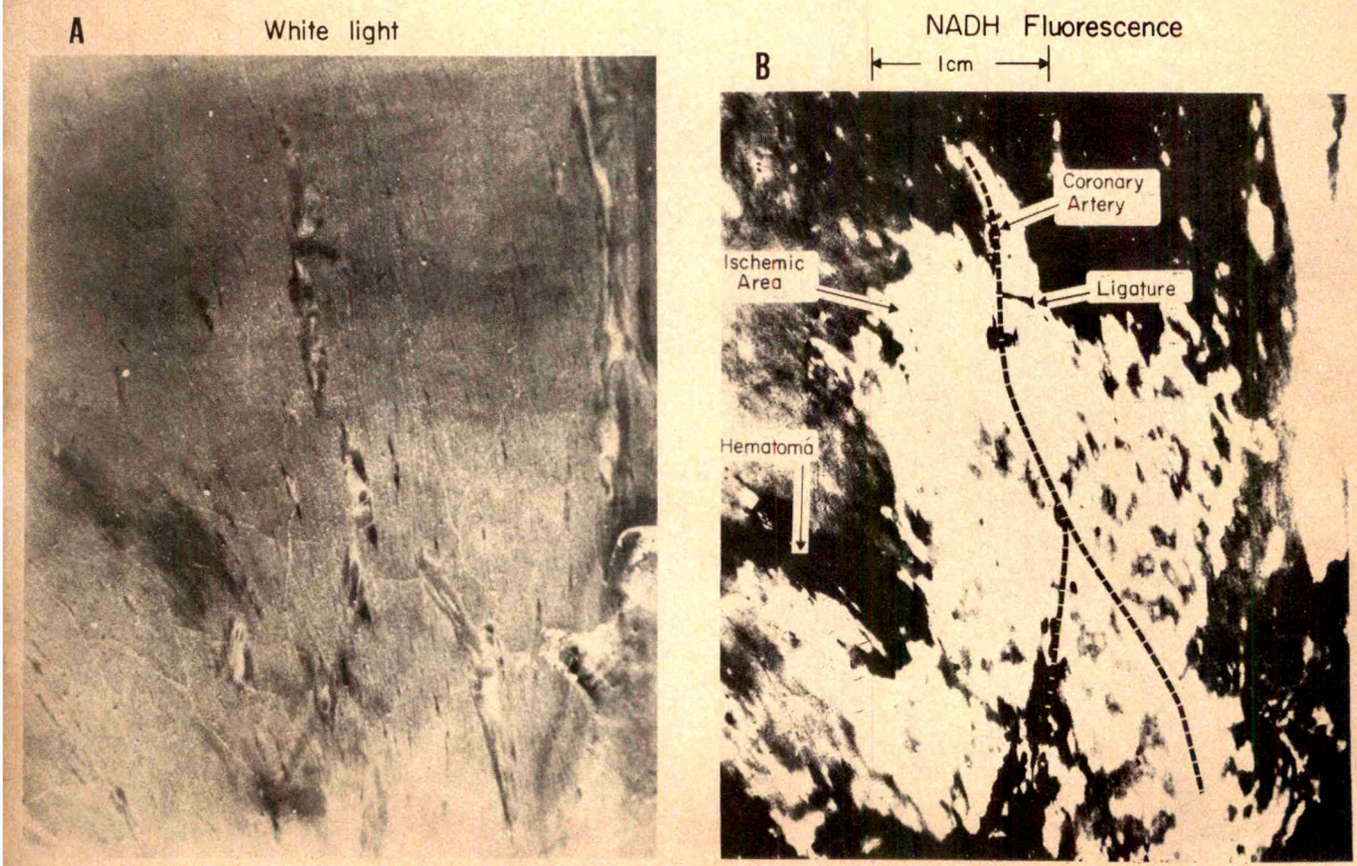


FIGURE 2. Rapid-frozen ischemic zone of canine left ventricle. **A,** white light photograph. The epicardium has been shaved off. The course of the coronary artery and level of the ligature are seen. It is difficult to appreciate the demarcation between normoxic and ischemic tissue. **B,** NADH fluorescence photograph. The ischemic zone is seen below the coronary ligature. The brightly fluorescent ischemic area is distinguished from the dark well oxygenated myocardium. The transition from NADH-fluorescent tissue to dark perfused tissue is abrupt (less than 0.1 mm). Islands of nonfluorescent tissue are seen within the zone of NADH ischemic fluorescence.

to be the same, and Linder[16] confirmed a very steep decrease in blood flow within a narrow surrounding border zone. Similarly, Hirzel et al.[6] found homogeneous creatinine phosphokinase depletion throughout ischemic myocardium with normal creatinine phosphokinase activity immediately adjacent to this area.

Characteristics of the ischemic border zone: The results of the present study delineate the ischemic border fluorophotographically. NADH was used as a natural intracell marker that, when fluorescent, indicated insufficient tissue oxygen supply. Incident light is filtered to the wavelength for NADH excitation, and

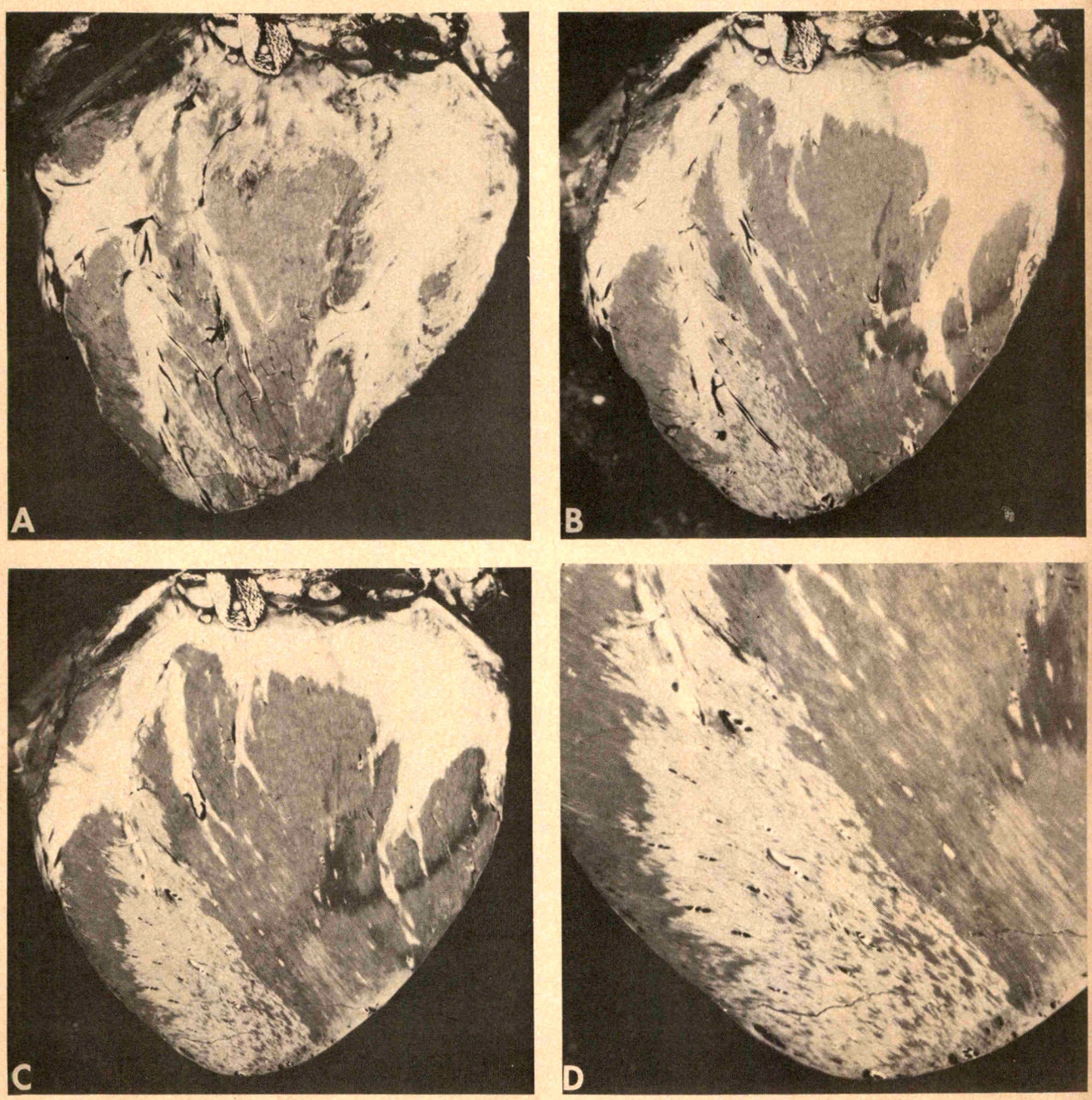


FIGURE 3. NADH fluorescence photographs of a rapid-frozen isolated decompressed heart 5 minutes after ligation of a diagonal branch of the left anterior descending coronary artery. **A,** the outer 0.5 mm of epicardium has been shaved off. Fat and vascular collagen fluoresce brightly. Zones of bare perfused ventricular myocardium are nonfluorescent. Small areas of NADH ischemic fluorescence are seen distal to the ligature. **B,** 1.0 mm of epicardium shaved off. The peninsula of NADH fluorescence distal to the coronary ligature is larger with increasing distance into the myocardium. The transition between perfused and ischemic tissue is abrupt and the borderline is jagged. Islands of normoxic tissue are seen within the ischemic zone. **C,** 1.5 mm of epicardium shaved off. The NADH fluorescent ischemic zone continues to increase in size with distance into the myocardium. The abrupt, jagged ischemic border is again evident as are the normoxic islands within the ischemic zone. **D,** same specimen as in **C,** magnified ×2. The abrupt transition from NADH ischemic fluorescence to nonfluorescent normoxic tissue is confirmed.

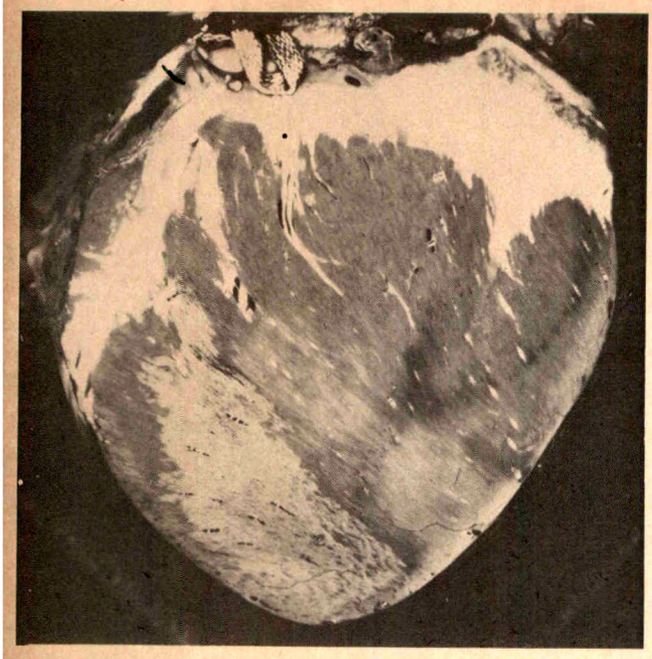


FIGURE 4. Same specimen as in Figure 3 with 8 mm of epicardium and myocardium shaved off. The NADH-fluorescent ischemic zone persists and is well seen. Within the adjacent zone of perfused tissue is a diffuse area of NADH fluorescence. This is interpreted as freezing artifact. During the several seconds required to freeze this tissue, oxygen demand exceeds supply and NADH becomes reduced. A smaller zone of freezing artifact is evident at 1.5 mm in Figure 3C.

fluorescence between 430 and 510 nm represents accumulation of NADH from ischemic tissue.[17,18] The transition between NADH-fluorescent and nonfluorescent zones is always abrupt (less than 0.1 mm). The ischemic margin is not smooth but jagged. Within the border of NADH-fluorescent tissue there are islands of nonfluorescent cells measuring 0.5 mm in diameter. These islands have a central fluorescent core. Figure 2B represents an abrupt transition between perfused (NADH-nonfluorescent) and ischemic (NADH-fluorescent) tissue. Within the ischemic zone, we interpret this figure to indicate coronary collateral vessels, each surrounded by an island of normoxic tissues that have been cut in cross section. The core of these islands fluoresce because of the presence of vascular collagen. The cells just outside these islands are as fluorescent, and therefore as ischemic and as jeopardized, as the NADH-fluorescent tissue just within the other outer ischemic margin. Viable islands at the ischemic border have been demonstrated histologically by Jennings[19] and confirmed with an autoradiographic technique by Cohn et al.[20] That group[21] recently developed three dimensional reconstructions of serial sections through the ischemic border. They found no true viable islands but, instead, interdigitating peninsulas of normoxic tissue probably surrounding coronary collateral vessels in the border zone. Evidence from our study conforms exactly with these observations.

Transition from normally perfused and hypoxic tissue at the border zone: Sugano et al.[22] titrated NADH with oxygen and found a rapid reduction of NAD over a small oxygen gradient at very low oxygen concentrations. As oxygen concentration decreases from 10^{-7} to 10^{-8} molar, NAD converts from 80 percent oxidized to 70 percent reduced. Fluorophotographically, tissues either do or do not appear to fluoresce. There is very little grey zone because the oxygen tension gradient is so steep at the ischemic border. In this study, intra-arterial oxygen tension was approximately 85 torr. NAD becomes reduced and fluoresces when the ambient oxygen tension falls below 10^{-7} molar (0.07 torr).[23] The distance between a perfused arteriole and NADH-fluorescent tissue is less than 0.1 mm. Thus, the oxygen gradient is at least (probably greater than) 0.1 torr/micron.

The transition between NADH-fluorescent and nonfluorescent zones is always abrupt. In dogs, however, the distance between homogeneously nonfluorescent and homogeneously fluorescent areas (no interspersed perfused islands) may be 6 to 8 mm. A similar examination of regional myocardial oxygen supply was carried out in the perfused rat and rabbit heart.[24] The border zone was examined fluorophotographically with computerized light-guide scanning and with microanalytical biochemical techniques. The transition from 80 percent oxidized NAD to 80 percent reduced NADH occurred within a distance of 150 μ. This was confirmed by biopsy microanalysis of NADH concentrations.[24]

No difference in the pattern of the ischemic border zone (epicardial or myocardial) was observed in specimens from the isolated perfused hearts and in hearts in intact open chest animals. The area of the ischemic zone clearly expanded down into the myocardium toward the endocardium in both preparations.

Problem of freezing artifact: We were concerned about the problem of freezing artifact. Intramyocardial tissue that was not frozen sufficiently rapidly might become reduced during the freezing process, producing spuriously large zones of NADH-fluorescent tissue. This problem has been evaluated in quick-frozen liver[25,26] and brain.[26,27] The investigators found stable oxidation-reduction potentials within tissue up to 1.0 mm below the surface of liquid nitrogen-fixed specimens. In our study, the freezing artifact is visible (Fig. 4). This specimen was taken 8 mm below the epicardial surface. Adjacent to the NADH-fluorescent ischemic zone is a blush of fluorescence due to slow freezing. This blush is also visible in the sections of the same heart taken at 1.5 mm (Fig. 3, C and D). However, the pattern of the ischemic zone and border remains clear. We believe, therefore, that freezing artifacts do not contribute to the NADH-fluorescent pattern of sections taken within 1 mm of the epicardial surface.

Implications: Tissue metabolic microheterogeneity is normal in many organs. The traditional approach to the delineation of ischemic and peri-ischemic zones has been to average the biochemical,[4,5] histochemical[3] and electrophysiologic[1] characteristics of a myocardial

sample volume. Until recently, the spatial resolution of these techniques was limited by the sample size (usually 3 to 4 mm). Fluorophotographic methods permit high resolution two dimensional evaluation of epicardial and myocardial oxidation-reduction states. It appears that the intramyocardial ischemic border in the dog may be defined in two ways. First, the distance between NADH-fluorescent ischemic cells and adjacent nonfluorescent cells is less than 0.1 mm. Second, the distance between homogeneously NADH-fluorescent tissue and homogeneously nonfluorescent tissue (across the zone of island normoxia) may be as wide as 6 to 8 mm.

Acknowledgment

We are grateful to David Reale for technical assistance and to Nancy Wells for secretarial assistance.

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Superiority of Practolol Versus Propranolol in Protection Against Ventricular Fibrillation Induced by Coronary Occlusion

DAVID L. PEARLE, MD, FACC
DANIEL WILLIFORD
RICHARD A. GILLIS, PhD

Washington, D.C.

The ability of practolol and propranolol to prevent ventricular fibrillation in experimental anterior myocardial infarction was compared in dogs subjected to ligation of the left anterior descending and first septal coronary arteries. This procedure, which causes ventricular fibrillation in 90 percent of animals within 30 minutes, was performed in control dogs and in dogs pretreated with propranolol (0.5 mg/kg body weight) or with practolol (1.5 to 2.5 mg/kg). These doses produced nearly equivalent shifts in isoproterenol-induced chronotropic dose-response curves, indicating equivalent degrees of beta adrenergic blockade. In 21 dogs with confirmed ligation, cardiogenic shock did not develop. Six of seven control dogs died with ventricular fibrillation. Six of seven dogs pretreated with propranolol also had fibrillation, whereas only one of the seven dogs pretreated with practolol manifested ventricular fibrillation during the 45 minute postligation observation period. Practolol afforded significant protection compared with no treatment or treatment with propranolol ($P < 0.05$).

A large prospective study recently demonstrated that the cardioselective beta adrenergic receptor blocking agent practolol decreases long-term mortality in patients after anterior myocardial infarction.[1,2] This study has received considerable attention because of its potential clinical importance. Practolol is unlikely to be approved for further clinical use because of adverse effects (sclerosing peritonitis, cutaneous and ocular reactions and a lupus erythematosus-like syndrome), and propranolol is the only beta blocking agent now approved for clinical use in the United States. Therefore, the National Institutes of Health are beginning a large scale study to test the effect of propranolol in preventing death from coronary disease.[3]

However, there is evidence to suggest that practolol may be more effective than propranolol in decreasing the number of deaths from heart disease. Marshall and Parratt[4] compared the two agents in equivalent beta adrenoreceptor blocking doses and found that practolol, in contrast to propranolol, benefited the ischemic myocardium as demonstrated by electrocardiographic criteria, lactate measurements, myocardial temperature changes and myocardial oxygen consumption data.

This study compared the ability of the cardioselective beta blocking agent practolol with the noncardioselective agent propranolol in equivalent beta adrenoreceptor blocking doses to prevent ventricular fibrillation after acute coronary occlusion.

Methods

Experimental procedure: Mongrel dogs unselected for sex and weighing 10.5 to 22.5 kg were anesthetized with sodium pentobarbital (30 to 35 mg/kg body weight intravenously). Tracheal cannulation was performed and the animals were ventilated with a Harvard respirator pump (20 cc/kg, rate 18 to 20/

From the Departments of Pharmacology and Cardiology, Georgetown University Schools of Medicine and Dentistry, Washington, D.C. This work was supported in part by Grant NS-12566 and Division of Research Resources Bio-Medical Support Health Grant RR-05360 from the U.S. Public Health Service, Bethesda, Maryland. Manuscript received May 9, 1978; revised manuscript received June 20, 1978, accepted July 5, 1978.

Address for reprints: David L. Pearle, MD, Georgetown University Hospital, Division of Cardiology, 3800 Reservoir Road, NW, Washington, D.C. 20007.

TABLE I

Comparative Effects of Practolol and Propranolol on Arterial Blood Pressure, Heart Rate and Arrhythmias Induced by Coronary Occlusion

Group	Before Drug BP	Before Drug HR	After Drug BP	After Drug HR	Time to Onset of Ventricular Arrhythmia (min)	Time to Onset of VF (min)	Incidence of VF*
Control (7 dogs)	98 ± 11	152 ± 7	. . .	. . .	2.9 ± 0.3 (7)	12.0 ± 2.5 (6)	6/7
Practolol-treated (7 dogs)	120 ± 6	182 ± 16	120 ± 6	125 ± 7†	8.0 ± 2.6 (6)	4.0 (1)	1/7‡
Propranolol-treated (7 dogs)	115 ± 7	196 ± 15	118 ± 5	138 ± 5†	5.2 ± 2.0 (6)	8.8 ± 2.7 (6)	6/7

* Number of dogs with ventricular fibrillation/number of animals in treatment group.
† $P < 0.05$ using the paired t test.
‡ $P < 0.05$ using either the Fisher's exact test or the chi square distributing test with the Yates correction factor.
BP = blood pressure (mm Hg); HR = heart rate (beats/min); VF = ventricular fibrillation.

min). Rectal temperature was monitored and maintained between 36° and 38°C with radiant heat. Lead II of the electrocardiogram was monitored continuously throughout the experiment using a Brush recorder. Arterial blood pressure was recorded from a femoral arterial catheter attached to a Micron Instruments blood pressure transducer. A catheter was placed in the femoral vein for drug injection. Both cervical vagus nerves were sectioned to provide an infarction model exhibiting a high rate of ventricular fibrillation,[5,6] and to permit assessment of the degree of beta adrenergic blockade using isoproterenol as the agonist without interference from reflex-induced changes in efferent vagal tone. A left thoracotomy was performed, and the left anterior descending and first septal coronary arteries were exposed and occluded. This infarction model, previously used by Myers et al.,[5] is described in greater detail in their report. Animals exhibiting a decrease in mean blood pressure equal to 50 percent of the initial blood pressure (defined as shock) were excluded from the data analysis. This occurred in only three dogs, one in the control group and one each in the two pretreatment groups. The dogs were observed until ventricular fibrillation occurred or for 45 minutes after coronary arterial ligation.

Pretreatment with practolol or propranolol: Both d,l-practolol and d,l-propranolol (gift from Ayerst Drug Company, courtesy of Mr. Roy Grant) were used and considered to represent a cardioselective beta blocking agent and a noncardioselective beta blocking agent, respectively. The drugs were administered in doses producing roughly equivalent degrees of beta adrenergic blockade as determined by using shifts in the positive chronotropic dose-response curve induced by three doses of isoproterenol. In seven dogs pretreated with practolol (dose range 1.5 to 2.5 mg/kg), an average shift of 12.1 ± 1.7-fold (mean ± standard error of the mean) in the dose-response curve was observed. The seven dogs pretreated with propranolol (0.5 mg/kg) exhibited a 16.2 ± 2.5-fold shift ($t = 1.38$, $P > 0.05$) in the dose-response curve. The degree of shift in the curves approximated the shift reported by Marshall and Parratt[4] in their study documenting differences in the effects of practolol and propranolol during ischemia.

Results

Effect on incidence of ventricular fibrillation: The most important finding of our study was that administration of the cardioselective beta adrenergic blocking agent practolol protected animals subjected to coronary occlusion from ventricular fibrillation. Ventricular fibrillation developed in only one of seven dogs pretreated with this agent (Table I), although it occurred in six of seven dogs in the control group. Perhaps equally important was the observation that administration of the noncardioselective beta adrenergic blocking agent propranolol had no significant effect on the incidence of ventricular fibrillation (Table I). Indeed, dogs pretreated with propranolol did not differ from the control dogs in the cardiac rhythm disturbances that developed after coronary occlusion. Despite these differences in effect between propranolol and practolol in protecting against ventricular fibrillation, there were no differences in severity of premonitory ventricular arrhythmias (using the Lown grading system)[7] between control, propranolol-treated and practolol-treated groups. All dogs had frequent multifocal and early ventricular premature complexes with couplets. One control dog, two dogs treated with practolol and one dog treated with propranolol had couplets but not salvos of ventricular beats, and three of those four dogs survived.

Other cardiovascular effects: In spite of the striking difference between the effect of the two types of beta adrenergic blocking agents on the incidence of ventricular fibrillation, there was, with one exception, no other significant difference in the cardiovascular responses of dogs pretreated with these two drugs. At the doses used, both agents produced a significant decrease in sinus rate but no significant change in mean blood pressure. Similarly, the decrease in mean arterial blood pressure that occurred after occlusion did not differ significantly in the two drug treatment groups (Fig. 1). Most importantly, there was no significant difference between the two groups in the magnitude of the decrease in diastolic blood pressure that regularly occurred after coronary occlusion. The decrease in diastolic pressure ranged from 11 ± 2 to 15 ± 2 mm Hg in

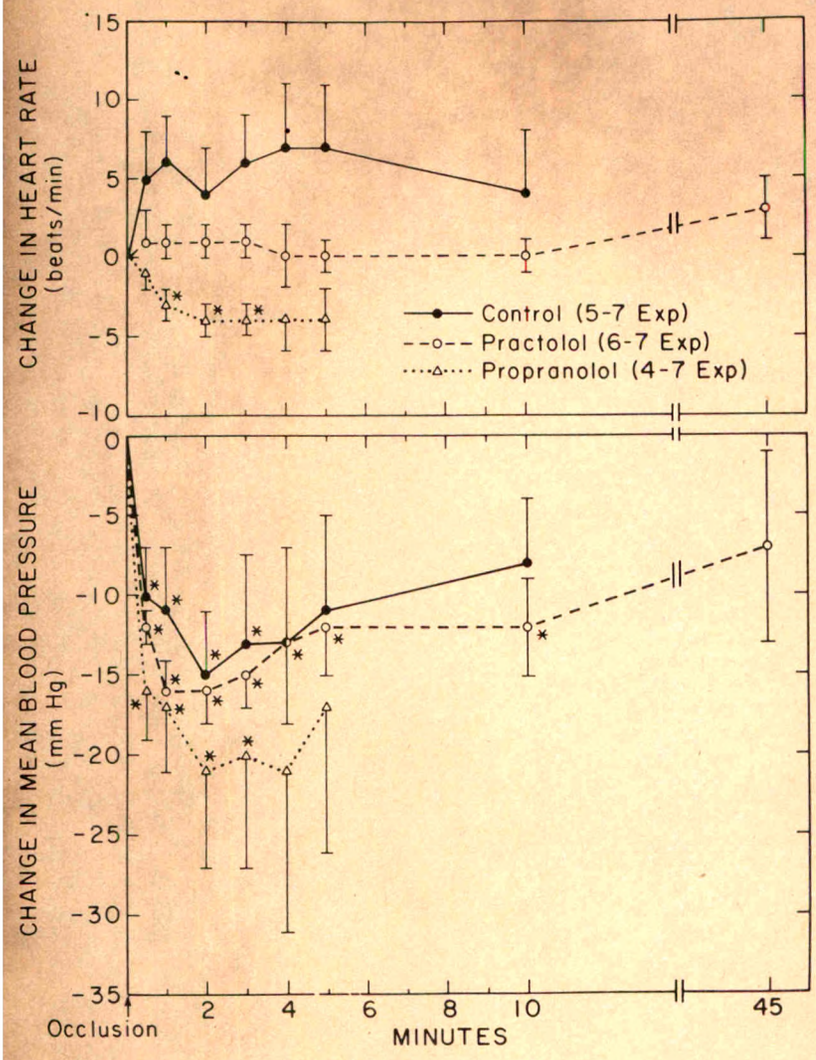


FIGURE 1. Effect of pretreatment with practolol and propranolol on the changes in heart rate and arterial blood pressure produced by coronary occlusion (as indicated by the **arrow** at time zero). **Asterisks** indicate significant changes produced by coronary occlusion ($P < 0.05$ using paired t statistic). Exp = experiments.

the practolol-treated group and 15 ± 3 to 20 ± 6 mm Hg in the propranolol-treated group (over the first 5 minutes after occlusion). The one difference that was observed between the drug-treated groups was in the sinus rate response produced by occlusion. The propranolol-treated dogs exhibited a significant decrease in rate after occlusion, whereas both the practolol-treated and control groups had no significant change in sinus rate after occlusion (Fig. 1).

Survival and late effects: The effects of occlusion on the cardiovascular indexes measured were observed for 45 minutes. At this time only one animal remained alive in the control and propranolol-treated groups, whereas six animals survived in the practolol-treated group. In the single survivor in the control group, mean pressure and heart rate were reduced by 14 mm Hg and 21 beats/min, respectively. Corresponding values for the single surviving dog in the propranolol-treated group were an increase of 18 mm Hg and a decrease of 4 beats/min. In the six surviving dogs treated with practolol, mean arterial pressure and sinus rate 45 minutes after occlusion had returned to baseline level and were not significantly different from the values obtained before ligation (Fig. 1).

Discussion

The effects of practolol and propranolol in experimental myocardial infarction were previously compared by Marshall and Parratt,[4] who administered the drugs in approximately equivalent doses (about 15-fold shift of the isoproterenol-induced chronotropic dose-response curve) to dogs 2 to 3 hours after occlusion of the left anterior descending cororary artery. Propranolol resulted in the following deleterious effects: (1) reduction of blood flow in the ischemic region; (2) increased S-T segment elevation; (3) increased left ventricular end-diastolic pressure; and (4) failure of ischemic myocardium to improve lactate production. In contrast, practolol had beneficial effects on ischemic myocardium: (1) Blood flow to ischemic myocardium was not reduced; (2) S-T elevation decreased; (3) left ventricular end-diastolic pressure was not increased; and (4) lactate production was reversed.

In our study we compared the ability of these doses of propranolol and practolol to prevent ventricular arrhythmias in a similar experimental model of myocardial infarction. Although the frequency and severity of premature ventricular complexes and ventricular

tachycardia did not vary, practolol largely prevented ventricular fibrillation, whereas equivalent beta blocking doses of propranolol did not. Indeed, the dramatic protective effects of practolol in our study are emphasized by comparison with those of lidocaine in another study using the same model.[8] In the lidocaine study, 6 of 11 animals were protected from fibrillation, whereas in our study 6 of 7 animals pretreated with practolol survived. Although it is difficult to compare studies from different laboratories, it is interesting that in the same model practolol in our study was even more effective than lidocaine in another study.

Comparison with previous studies: Our finding that practolol did not protect animals from ventricular fibrillation is consistent with previous data obtained from cats subjected to left anterior descending coronary arterial occlusion.[9] In that study pretreatment with propranolol, in slightly larger doses, had no effect on the incidence of ventricular fibrillation in either vagotomized or nonvagotomized cats. However, other investigators[10–12] have reported that pretreatment with propranolol reduces the incidence of ventricular fibrillation in dogs subjected to coronary occlusion. They found that small doses of propranolol (0.08, 0.1 and 0.25 mg/kg) were effective, whereas in some studies[10,12] larger doses (0.2 and 1.0 mg/kg) were ineffective. However, a dose difference does not seem to be the critical factor, because there is an overlap of reported "low" (0.08 to 0.25 mg/kg) and "high" (0.2 to 1.0 mg/kg) doses. Site of occlusion is a more likely explanation for the conflict between our study, which failed to show antiarrhythmic effects of propranolol, and others that demonstrated protection. We ligated the left anterior descending coronary artery and first septal perforator, whereas others ligated the left circumflex coronary artery[10,12] or used microspheres to occlude the entire coronary bed.[11] The influence of site of occlusion on the effects of antiarrhythmic drugs has previously been demonstrated,[13,14] and the anatomic location of infarction may be a critical difference.

Reasons for superiority of practolol over propranolol: The reasons for the superiority of practolol over propranolol in preventing ventricular fibrillation in our experimental model are yet to be determined. The data of Marshall and Parratt[4] suggest that the important difference may be that practolol benefits ischemic myocardium, whereas propranolol does not. However, most data suggest that propranolol has several potentially beneficial effects in acute myocardial infarction. Propranolol reduced myocardial oxygen demand by decreasing heart rate and contractile force,[15] and (in most studies) improved blood flow to ischemic areas.[16–18] In addition, it reduced infarct size[19] and (in most studies) reversed lactate production in ischemic areas.[20–22] These beneficial effects are clearly in contrast to the effects described by Marshall and Parratt and do not appear to be translated into a beneficial antifibrillatory response in our study. A possible explanation may be the effect of propranolol on ventricular preload. Marshall and Parratt observed an increase in left ventricular end-diastolic pressure in propranolol-treated animals, but no similar increase with practolol. Ventricular preload is a particularly critical factor in determining perfusion of ischemic areas after coronary occlusion.[23] In this setting, the coronary bed of the ischemic area is maximally dilated, and tissue perfusion should be directly dependent on the diastolic pressure gradient between the vessel distal to occlusion and the left ventricle. Increased left ventricular end-diastolic pressure would reduce this pressure gradient and result in underperfusion of the subendocardial region of the ischemic zone.[23] Thus, the difference between the effects of propranolol and practolol on left ventricular end-diastolic pressure may be significant and related to antiarrhythmic effects.

Clinical implications: Our data, although obtained from open chest anesthetized dogs, are consistent with data from clinical trials. With one early exception,[24,25] clinical studies to date[26–28] have not demonstrated reduced mortality after myocardial infarction in patients pretreated with propranolol, although this question has not been conclusively answered. In contrast, a well designed large prospective study comparing pretreatment with practolol versus placebo demonstrated a significant reduction in mortality,[1,2] at least for patients after anterior myocardial infarction. Thus, practolol is the beta adrenergic blocking agent whose protective effects have been most clearly demonstrated, although alprenolol has also been demonstrated to be protective in controversial studies.[29,30]

Our study is the first to compare the ability of propranolol and practolol to prevent ventricular fibrillation in experimental acute anterior myocardial infarction, and it demonstrates that propranolol does not share the salutary effects of practolol. The demonstrated differences between the two drugs suggest that cardioselectivity may be a critical factor, although other differences between these agents such as the degree of intrinsic sympathetic agonist activity may also be important. Adverse effects prevent the clinical use of practolol. However, newer cardioselective agents such as acebutolol, atenolol and metoprolol may prove to be more effective than propranolol for prophylaxis against ventricular fibrillation in patients with ischemic heart disease.

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Comparative Study of Two Methods of Estimating Sinoatrial Conduction Time in Man

GÜNTER BREITHARDT, MD
LUDGER SEIPEL, MD

Düsseldorf, West Germany

Programmed premature atrial stimulation has been widely used to estimate sinoatrial conduction time in man. A proposed new approach uses continuous atrial pacing just above the spontaneous cycle length. Sinoatrial conduction time is represented by the difference between the first cycle after pacing and the spontaneous cycle length, assuming that sinus nodal automaticity is undisturbed by continuous atrial pacing.

Both techniques were compared in 23 consecutive patients. Mean (± standard deviation) sinoatrial conduction time was 113 ± 27 msec estimated with the premature stimulus technique and 96 ± 48 msec when estimated with the continuous pacing technique. In about 30 percent of cases the two values corresponded well with each other. In the remaining patients sinoatrial conduction time estimated with the premature stimulus technique was longer than the time estimated with continuous atrial pacing. Additionally, the latter was estimated at two different rates of pacing in which the cycle length was 30 and 60 msec, respectively, shorter than the previous cycle length. The estimate then increased to 119 ± 39 and 136 ± 40 msec, respectively. Sinoatrial conduction time estimated with continuous atrial pacing did not depend on spontaneous cycle length and did not correlate with sinus nodal recovery time. The cycles after the first pause were slightly longer than the spontaneous cycle length.

The results suggest that data from the two techniques cannot be easily compared and that premature atrial stimulation may exert a more depressive effect on sinus nodal automaticity than continuous atrial pacing. The observed differences in results may also be due to a more pronounced delay of retrograde conduction during premature atrial stimulation than during continuous atrial pacing. It is also possible that continuous atrial pacing leads to some overdrive exciting effect on the sinus node, although the opposite effect is suggested by the response of the cycles after the first postpacing cycle. A final conclusion regarding the validity of each technique cannot be reached on the basis of these clinical data.

Direct recording of sinus nodal potentials, although under study, has not yet been accomplished in man. Therefore, sinoatrial conduction time can only be estimated indirectly. Many clinical studies have used premature atrial stimulation for indirect estimation of sinoatrial conduction time[1–11] as originally proposed by Strauss et al.[12] Recently, Narula et al.[13,14] proposed a new approach to the assessment of sinoatrial conduction time using continuous atrial pacing instead of premature atrial stimuli. To test whether the two methods give comparable results and to elucidate the factors that might influence the validity of this new approach, we studied 23 patients with both stimulation techniques.

Methods

All patients were studied in the catheterization laboratory in the nonsedated postabsorptive state after having given written informed consent. The studies were indicated for clinical reasons. Catheter positioning and recording techniques have been described previously.[1,15,16]

From the Medical Clinic, Department B (Cardiology), The University of Düsseldorf, West Germany. Manuscript received March 22, 1978; revised manuscript received June 14, 1978, accepted July 19, 1978.

Address for reprints: Günter Breithardt, MD, Med. Klinik und Poliklinik, Klinik B, Schwerpunkt Kardiologie, Moorenstrasse 5, D 4000 Düsseldorf, West Germany.

TABLE I

Clinical Diagnosis and Electrophysiologic Data (in msec) in 23 Patients

Case no.	Age (yr) Sex	Clinical Diagnosis	SCL Preceding Estimation of SNRT (mean ± SD)	$SNRT_{max}$	SNRT at Lowest Rate of Overdrive Pacing	$CSNRT_{max}$
1	71M	LAH, APC, syncope	679 ± 14.2	878	856	199
2	48M	Idioventricular rhythm	1055 ± 44.2	1409	1409	354
3	79M	LAH, RBBB, APC	866 ± 21.5	1164	1164	298
4	58F	SB (36 beats/min)	1128 ± 19.7	1853	1378	725
5	47M	VPC, syncope	844 ± 26.0	1304	1169	460
6	45M	LBBB	867 ± 21.4	1256	1126	389
7	42M	Ventricular tachycardia	630 ± 15.9	1188	779	558
8	38F	WPW type A, int AF	666 ± 21.5	1019	1019	353
9	37F	LBBB, 1° AVB	802 ± 17.5	1011	886	209
10	50M	Int 3° AVB, SB (40 beats/min)	1034 ± 31.4	1472	1375	438
11	52F	LGL	903 ± 43.8	1362	1116	459
12	45M	Syncope of unknown origin	904 ± 29.7	1380	1173	476
13	63M	SB (45 beats/min) int AF, VPC	1156 ± 57.4	1577	1340	421
14	35F	LBBB	744 ± 21.2	1245	1205	501
15	39F	LBBB, APC	803 ± 27.8	1031	1022	228
16	40M	APC with anterograde block	807 ± 23.2	1221	1200	414
17	57F	SA block, VPC	725 ± 9.7	1300	1002	575
18	23F	Romano-Ward syndrome	856 ± 72.2	944	944	88
19	17F	SB (40 beats/min)	929 ± 82.9	1480	1271	551
20	51F	LBBB, VPC, APC	739 ± 46.1	1104	901	365
21	19M	AVB, 1° and 2°, type I	851 ± 36.7	1159	1084	308
22	58M	VF	859 ± 19.8	1331	1122	472
23	27M	VF	605 ± 17.1	768	768	163
Mean ±SD	45.3 ±15.5		837.0 31.3 ±151.6 ±18.8	1237.2 ±243.1	1100.4 ±187.9	413.3 ±161.5

AF = atrial fibrillation; APC = atrial premature complexes; AVB = atrioventricular block (1°, 2° and 3° = first, second and third degrees, respectively); $CSNRT_{max}$ = maximal corrected sinus nodal recovery time; Int = intermittent; LAH = left anterior hemiblock; LBBB = left bundle branch block; LGL = Lown-Ganong-Levine syndrome; RBBB = right bundle branch block; S-A = sinoatrial; SB = sinus bradycardia; SCL = spontaneous cycle length; SD = standard deviation; SNRT and $SNRT_{max}$ = sinus nodal recovery time and maximal sinus nodal recovery time, respectively; VF = ventricular fibrillation; VPC = ventricular premature complexes; WPW = Wolff-Parkinson-White syndrome.

TABLE II

Results of Premature Atrial Stimulation (in msec)

Case no.	A_1-A_1 (mean ± SD)	$SACT_P$	A_3-A_4 minus A_1-A_1
1	659 ± 11.5	69	3
2	1056 ± 41.6	97	−5
3	866 ± 14.6	127	0
4	1129 ± 18.4	149	43
5	848 ± 32.3	144	7
6	866 ± 32.9	121	13
7	631 ± 21.9	112	−18
8	668 ± 15.7	140	16
9	802 ± 34.8	87	−8
10	1024 ± 48.3	125	30
11	900 ± 68.7	106	63
12	891 ± 27.0	117	18
13	1127 ± 34.9	129	6
14	748 ± 15.6	87	−26
15	810 ± 10.8	89	33
16	829 ± 37.3	173	38
17	727 ± 8.9	65	39
18	821 ± 44.8	90	22
19	962 ± 54.3	145	−23
20	725 ± 17.9	110	−3
21	872 ± 26.9	105	36
22	839 ± 11.7	126	−3
23	611 ± 15.2	89	1
Mean ±SD	844 ±145.4 28.1 ±15.9	113.1 ±27.1	12.3 ±22.9

$SACT_P$ = sinoatrial conduction time estimated with the premature atrial stimulation method; SD = standard deviation.

Premature atrial stimulation method: Premature atrial stimuli were applied after each eighth spontaneous atrial cycle beginning late in diastole. The coupling intervals were decreased (in decrements of 10 msec) until the effective refractory period of the right atrium was reached. All atrial intervals were measured with an automatic interval counter (developed in collaboration with H. Mescher, IFD, Mülheim/Ruhr, West Germany) and printed on a digital printer (Kienzle). The accuracy of triggering could easily be controlled by simultaneously recording a trigger signal in the original electrocardiogram.

Data were then transferred by means of a teletype to a computer for normalization of cycle lengths and for plotting the normalized return cycles (A_2-A_3) versus the normalized coupling intervals of the premature complexes (A_1-A_2). The plateau zone (zone of reset of the sinus node) was chosen as an area of interest for calculation of sinoatrial conduction time, as previously described.[1,12,15] Sinoatrial conduction time (SACT) is half the difference between the mean return cycle (A_2-A_3) during the plateau zone and the mean spontaneous cycle length (A_1-A_1). It will be referred to as $SACT_P$ (P indicating the premature stimulus technique). Additionally, the postreturn cycles (A_3-A_4) were measured.

Continuous atrial pacing method: Sinoatrial conduction time, estimated by continuous atrial pacing, as proposed by Narula et al.,[13,14] will be referred to as $SACT_C$ (C indicating continuous pacing method). It was estimated as follows: The right atrial appendage was paced for nine cycles at a cycle length slightly shorter than the spontaneous cycle length. If atrial capture was not achieved consistently because of variation in spontaneous cycle length, the pacing cycle length was

shortened in decrements of 10 msec until consistent capture of the atrium was achieved. Pacing was then stopped to allow the spontaneous sinus rhythm to recur. This spontaneous rhythm was recorded during at least 10 cycles before pacing was resumed. The spontaneous cycles after pacing were labeled cycles 1 to 10. This sequence was repeated at least 10 times at the same rate of pacing. It was then repeated at two pacing cycle lengths that were, respectively, 30 and 60 msec shorter than the first pacing cycle length. These three pacing cycle lengths were consecutively labeled cycle length 1, 2 and 3. Sinoatrial conduction time (continuous pacing method) was calculated from the length of the first cycle after stimulation (cycle 1) and the mean of 10 spontaneous cycle lengths ($\overline{SCL}$) immediately preceding the onset of pacing at the three different rates, according to the following equation:

$$SACT_C = \frac{\text{cycle 1 minus } \overline{SCL}}{2}.$$

Sinus nodal recovery time was estimated using high rate atrial pacing at rates from 60 (if possible) up to 200 beats/min at increments of 20 beats/min for 30 seconds. The interval between two pacing periods was at least 15 seconds to allow the spontaneous sinus rhythm to resume. Sinus nodal recovery time was corrected for rate by subtracting the mean of the spontaneous cycles immediately preceding pacing.

Statistical evaluation was performed using Student's *t* test for paired data; regression analysis was performed using a computer program.

Results

The clinical data and electrophysiologic findings in the 23 patients are given in Table I. The mean age (± standard deviation) was 45.3 ± 15.5 years. All patients had sinus rhythm at a mean spontaneous cycle length of 837 ± 161.6 msec (range 605 to 1,156 msec). Five patients had sinus nodal dysfunction as manifested by sinus bradycardia or sinoatrial block (or both) or intermittent atrial fibrillation.

The results of estimation of sinoatrial conduction time with the premature atrial stimulus and continuous atrial pacing methods are shown in Tables II and III, respectively. Figure 1 gives a typical example of the estimation using continuous atrial stimulation. The mean of 10 spontaneous cycles before pacing was 679 ± 16 msec. Atrial pacing was first performed at a cycle length of 660 msec. The first cycle after stimulation was 790 msec. If one assumes that the sinus node was captured by the last paced beats, the length of the first cycle after pacing (cycle 1) was composed of retrograde and anterograde sinoatrial conduction and the cycle length of the sinus node. Provided that no change in sinus nodal automaticity occurred, sinoatrial conduction time (continuous pacing method) was 55.5 msec. The mean value of sinoatrial conduction time (continuous method) after 10 runs of pacing was 81 msec. Sinoatrial conduction time (premature stimulus technique) was 69 msec in this patient.

Mean sinoatrial conduction time (continuous pacing method) at cycle length 1 in all 23 patients was 96 ± 48 msec (Table III), whereas with the premature stimulus technique it was 113 ± 27 msec (difference not signifi-

TABLE III

Results of Continuous Atrial Pacing (in msec)

Case no.	SCL Preceding CL 1	CL 1	Rate of Stimulation (beats/min)	$SACT_C$ At CL 1 (± SD)	Cycle 2 Minus SCL	SCL Preceding CL 2	$SACT_C$ At CL 2	SCL Preceding CL 3	$SACT_C$ At CL 3
1	646 ± 4.6	660	91	81 ± 12.4	16	645 ± 11.6	97	648 ± 7.9	130
2	1019 ± 25.9	1000	60	83 ± 17.7	21	1067 ± 23.0	119	1035 ± 25.6	85
3	876 ± 19.3	850	71	43 ± 11.8	−3	867 ± 14.5	97	885 ± 23.1	164
4	1127 ± 13.0	1100	55	56 ± 21.2	−7	1110 ± 14.7	88	. . .	. . .
5	843 ± 22.5	820	73	126 ± 3.0	10	. . .	. . .	866 ± 29.8	140
6	920 ± 44.9	850	71	92 ± 22.7	5	934 ± 15.5	125	969 ± 35.2	78
7	640 ± 24.0	620	97	63 ± 30.1	−5	645 ± 12.8	125	637 ± 16.8	148
8	682 ± 15.3	650	92	117 ± 23.8	24	659 ± 9.9	123	658 ± 12.9	146
9	777 ± 25.0	740	82	120 ± 31.0	72	802 ± 18.6	130	807 ± 27.3	149
10	1035 ± 19.0	1000	60	113 ± 33.5	44	1049 ± 26.4	133	1046 ± 26.6	134
11	898 ± 51.6	860	70	131 ± 36.9	107	889 ± 16.9	118	916 ± 53.1	134
12	882 ± 15.0	840	71	118 ± 20.2	29	856 ± 29.4	133	899 ± 26.8	142
13	1147 ± 25.0	1100	55	99 ± 44.5	30	1134 ± 28.0	128	1179 ± 68.2	158
14	722 ± 9.1	700	86	261 ± 16.5	52	725 ± 16.0	262	730 ± 32.9	248
15	824 ± 11.8	780	77	56 ± 22.1	4	812 ± 12.3	73	788 ± 13.9	66
16	822 ± 17.4	770	78	137 ± 25.8	−40	847 ± 20.6	147	817 ± 32.8	198
17	738 ± 14.0	700	86	61 ± 27.7	8	728 ± 5.6	89	710 ± 6.7	144
18	854 ± 43.2	800	75	85 ± 21.3	29	831 ± 33.2	132	818 ± 60.3	125
19	955 ± 51.0	900	67	138 ± 26.4	98	1009 ± 105.0	139	951 ± 69.6	141
20	742 ± 15.6	720	83	47 ± 20.8	−27	748 ± 44.8	83	721 ± 6.7	108
21	869 ± 18.3	820	73	57 ± 13.8	12	889 ± 26.3	104	850 ± 51.6	88
22	837 ± 11.5	820	73	86 ± 13.6	10	827 ± 5.5	115	819 ± 5.2	125
23	600 ± 13.6	570	105	39 ± 16.4	3	591 ± 18.3	59	. . .	. . .
							(no. = 22)	(no. = 21)	(no. = 21)
Mean ± SD	845.9 ± 22.2 149.4 ± 13.2	811.7 ±140.9	76.1 ±12.9	96.0 ± 22.3 ±48.0 ±9.2	21.4 ±35.1	848.4 ± 23.6 ±154.9 ±20.5	119.0 ±39.4	845.2 ± 30.1 ±140.6 ±19.9	135.8 ±40.3

CL 1, CL 2, CL 3 = cycle length 1, 2 and 3, respectively; $SACT_C$ = sinoatrial conduction time estimated with continuous atrial pacing; SCL = sinus cycle length; SD = standard deviation.

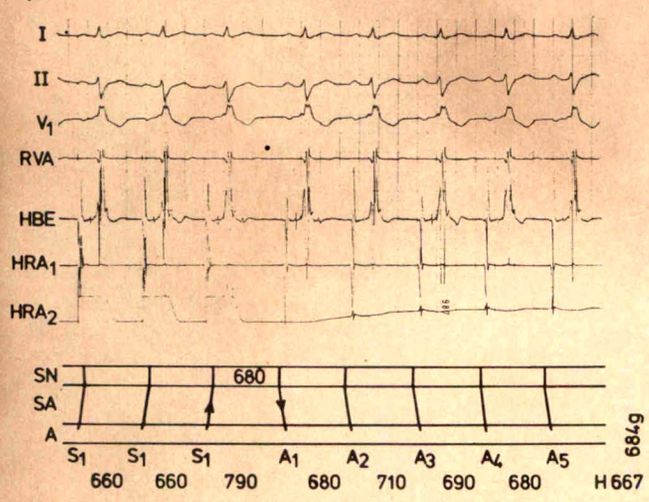


FIGURE 1. A typical example of the estimation of sinoatrial conduction time by continuous atrial pacing ($SACT_C$). After pacing of the high right atrium during nine cycles at a cycle length of 660 msec, a first pause emerged after pacing, represented by S_1-A_1, which was 790 msec long. This pause is composed of retrograde atriosinus nodal conduction time, the spontaneous cycle length of the sinus node and anterograde sinoatrial conduction time (see text). From the top down the tracings are electrocardiographic leads I, II, and V_1 and electrograms from the right ventricular apex (RVA), His bundle (HBE) and high right atrium (HRA_1 and HRA_2). A = atrium; SA = sinoatrial conduction; SN = sinus node. Numbers give cycle length in miliseconds.

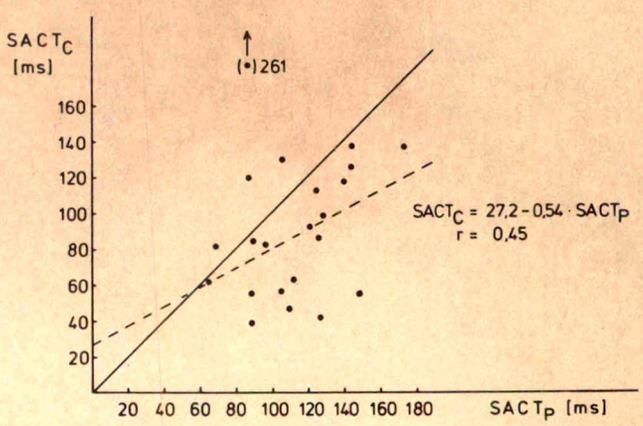


FIGURE 2. A plot of sinoatrial conduction time estimated with continuous atrial pacing ($SACT_C$) at the longest possible cycle length versus sinoatrial conduction time estimated with premature atrial stimulation ($SACT_P$). The coefficient of correlation between the two values is r = 0.45. ms = milliseconds.

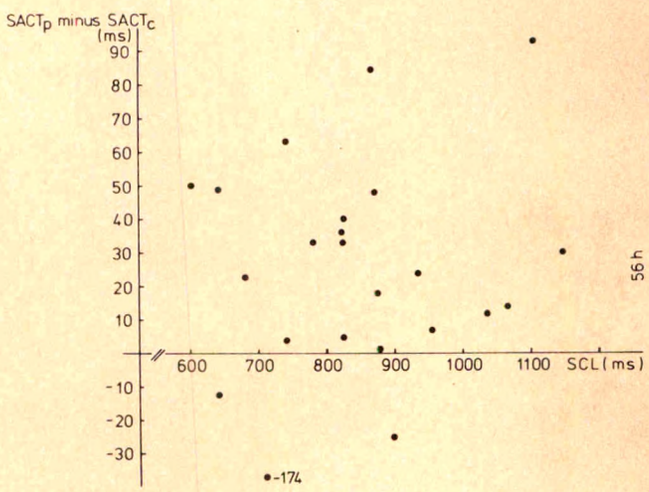


FIGURE 3. A plot of the difference between sinoatrial conduction time estimated with continuous atrial pacing and premature atrial stimulation ($SACT_P$ minus $SACT_C$) versus the spontaneous cycle (SCL). $SACT_P$ tended to be longer than $SACT_C$ at a shorter than at a longer spontaneous cycle length. The coefficient of correlation r = 0.17. ms = milliseconds.

cant) (Table II). However, with exclusion of Patient 14 the difference was significant (P <0.001). The mean prolongation of the postreturn cycles during the plateau zone versus the spontaneous cycle length was 12.3 ± 22.9 msec (Table II).

Sinoatrial conduction time: premature stimulus versus continuous pacing method: In Figure 2, sinoatrial conduction time estimated with the continuous pacing technique at the longest possible pacing cycle length is plotted against sinoatrial conduction time estimated with the premature stimulus technique. In seven cases (30 percent) the two values corresponded well (difference less than 14 msec), whereas in the remaining cases the value with the premature stimulus technique was distinctly longer than the value with the continuous pacing technique. In only one patient (Case 14) was sinoatrial conduction time estimated with the continuous pacing method much longer (261 msec) than that estimated with the premature stimulus technique (78 msec). This patient did not differ from the other patients with regard to electrophysiologic findings. The coefficient of correlation for the data in Figure 2 was r = 0.45.

Effect of cycle length of stimulation on sinoatrial conduction time (continuous pacing method): The cycle length of pacing was decreased by 30 and 60 msec, respectively. This resulted in a mean increase in the rate of pacing of 3.1 ± 1.06 beats/min with a range of 1.5 to 5.7 beats/min when considering the 30 msec decrease. In 15 cases the increase in the rate of pacing ranged between 2 and 4 beats/min. With a decreasing cycle length of stimulation, the sinoatrial conduction time increased in the majority of cases (Table III); at cycle length 2, it was 119 ± 39.4 msec (no. = 22), and at cycle length 3 it was 135.8 ± 40.3 msec (no. = 21). The increase in sinoatrial conduction time did not show any correlation with the different increases in the rate of atrial pacing.

Influence of spontaneous cycle length or sinus nodal recovery time on sinoatrial conduction time (continuous pacing method): In Figure 3 the difference between sinoatrial conduction time estimated with

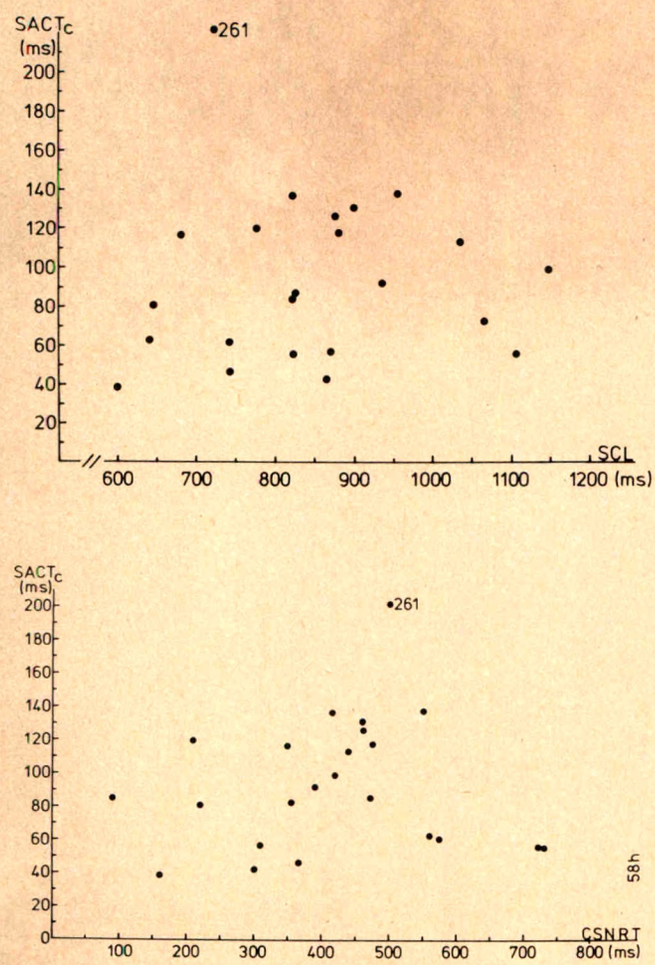


FIGURE 4. A plot of sinoatrial conduction time estimated with continuous atrial pacing ($SACT_c$) (at the longest possible cycle length of pacing) versus the spontaneous cycle length (SCL) **(top)** or versus corrected sinus nodal recovery time (CSNRT) **(bottom)**. ms = milliseconds.

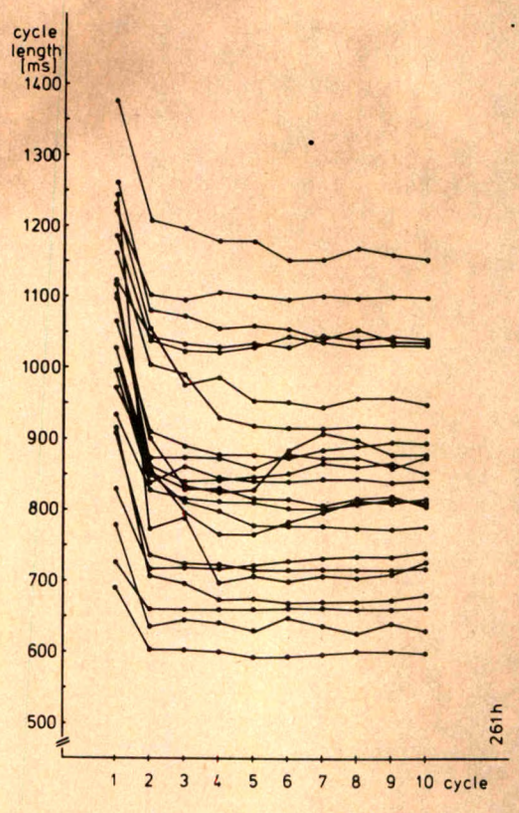


FIGURE 5. Lengths of the first 10 cycles (C_1 to C_{10}) after continuous atrial pacing in 23 patients. The dots represent the mean of 10 runs of pacing at the same rate. ms = milliseconds.

the premature stimulus technique and with the continuous pacing method (at the longest possible cycle length of pacing) was compared with the spontaneous cycle length. There was no statistically significant correlation between the two values, although the prolongation of sinoatrial conduction time estimated with the premature stimulus technique versus that estimated with the continuous pacing method tended to be more pronounced at shorter spontaneous cycle lengths in many patients. However, the coefficient of correlation was low ($r = 0.17$). Further, there was no correlation between sinoatrial conduction time estimated with the continuous pacing method at cycle length 1 and the spontaneous cycle length ($r = 0.0$) (Fig. 4, top) or corrected sinus nodal recovery time ($r = 0.1$; Fig. 4, bottom). The correlation was better when comparing sinoatrial conduction time estimated with the continuous pacing method at cycle length 3 with corrected sinus nodal recovery time ($r = 0.51$).

Spontaneous cycles after continuous pacing: In all cases the behavior of the first 10 cycles after cessation of continuous atrial pacing was studied. The values of 10 series of pacing were calculated and are graphically presented in Figure 5. The second cycle after pacing was, on average, 21.4 ± 35.1 msec longer than the spontaneous cycle length. In five of these cases (Cases 3, 4, 7, 16 and 20) cycle 2 was shorter than the spontaneous cycle length with differences ranging between −3 and −40 msec. In most cases the subsequent cycles were nearly identical with the spontaneous cycle length, for example, the third and fourth cycles after pacing were 7.3 ± 30.9 msec (−4.4 ± 25.1 msec longer or shorter than the spontaneous cycle length, respectively).

Discussion

Premature atrial stimulation for estimation of sinoatrial conduction time: The response of the sinus node to premature atrial stimuli has only recently been understood in some detail. Whereas some investigators[17,18] proposed that the pause after premature atrial stimulation was due to sinus nodal depression alone, others[12,19–21] suggested that it was due to sinoatrial conduction time. From the lengths of reset responses of the sinus node after premature atrial stimulation, Strauss et al.[12] calculated sinoatrial conduction time. The inherent methodologic limitations of this approach

have been amply discussed.[15,22–30] In spite of these limitations, assessment of sinoatrial conduction time with premature atrial stimulation has been of value in characterizing sinus nodal function in man.[1–11,16,31]

Continuous atrial stimulation for estimation of sinoatrial conduction time: Recently, Narula et al.[13,14] proposed this new approach. They suggested that the pause after a short period of continuous atrial pacing at a rate slightly above the spontaneous rate is composed of three intervals, the time for retrograde conduction from the atrium to the sinus node, the spontaneous cycle length of the sinus node and the anterograde sinoatrial conduction time. Provided that there is no change in sinus nodal automaticity after continuous atrial pacing, sinoatrial conduction time (both anterograde and retrograde) is represented by the difference between the first pause after pacing and the spontaneous cycle length. To establish whether premature atrial stimulation and continuous atrial pacing yield comparable results, we used both techniques in a cohort of 23 consecutive patients in whom His bundle studies were indicated for clinical reasons.

Comparison between sinoatrial conduction time estimated with premature atrial stimulation and continuous atrial pacing: Our data show that at the longest possible cycle length of pacing sinoatrial conduction time estimated with continuous pacing is usually shorter than that estimated with premature stimulation. There are several possible explanations for the differences between the two techniques. One possibility is that the sinus node is not discharged during the short period of atrial pacing because of the slow rate. However, this would cause the length of the first cycle after pacing to vary randomly to a great extent and this was not the case. Other possibilities include: (1) overdrive excitation of the sinus node[32,33] during continuous atrial pacing leading to underestimation of true sinoatrial conduction time or (2) overestimation of this interval with premature atrial stimulation because of an increase in retrograde conduction time or sinus nodal depression.

Overdrive excitation versus suppression during continuous atrial pacing: Atrial pacing for a long period of time has been widely used to estimate sinus nodal recovery time.[18,34] The underlying mechanism is overdrive suppression of sinus nodal activity.[35,36] With increasing rates of pacing, this overdriving effect increases until a decrease occurs at higher rates of pacing due to sinus nodal entrance block.[35] Therefore a pitfall in the estimation of sinoatrial conduction time with the method of Narula et al.[13,14] is that overdrive suppression of the sinus node might occur.

On the other hand, short periods of pacing at rates slightly above the spontaneous one may conversely lead to activation of automaticity in the sinus node[35] and in spontaneously beating Purkinje fibers.[32] This phenomenon has been called "overdrive excitation."[32,33] Idioventricular pacemaker cells demonstrated both overdrive excitation and suppression depending on the rate and duration of pacing. Overdrive excitation was likely to be observed when the cells were paced at a rate slightly above the spontaneous rate, whereas increasing the rate of pacing caused overdrive suppression.[32,33] Short periods of pacing usually elicited overdrive excitation whereas longer pacing led to overdrive suppression. The fundamental mechanisms regulating overdrive excitation are incompletely understood. Local activation of nerve endings and release of catecholamines have been discussed as the basic mechanisms.[32,33]

The question whether continuous atrial pacing during several cycles exerts a depressant or an exciting effect on the sinus node or has no effect at all cannot be answered directly from our data. In many patients the second cycle after cessation of continuous atrial pacing was still somewhat longer than the spontaneous cycle length before stimulation, which might be an indication of overdrive depression. The first pauses after cessation of continuous pacing were usually longer at shorter pacing cycle lengths than at the longest possible pacing cycle length. This prolongation might be due either to an increase in overdrive depression or to an increase in retrograde conduction time.[37] In any case, to avoid overestimation of sinoatrial conduction time with the continuous atrial pacing technique it seems crucial to pace at the longest possible cycle length.

Factors influencing the length of sinoatrial conduction time: Although there were some exceptions, sinoatrial conduction time estimated with either method correlated better in patients with long spontaneous cycle lengths; in patients with short spontaneous cycle lengths sinoatrial conduction time estimated with the premature stimulus technique was longer than that estimated with continuous atrial pacing (Fig. 3). This suggests either that premature atrial stimulation exerts a more depressant effect on sinus nodal automaticity at shorter spontaneous cycle lengths or that at relatively short spontaneous cycle lengths the premature impulse has to travel back toward the sinus node through the perinodal zone during its relative refractory period. A different possibility is that at shorter spontaneous cycle lengths the larger difference between both methods is due to underestimation of sinoatrial conduction time with continuous atrial pacing. However, because these data are not of statistical significance, this subject needs further elucidation in a greater number of patients.

The length of sinoatrial conduction time estimated with continuous atrial pacing was independent of spontaneous cycle length, a finding similar to the lack of correlation between sinoatrial conduction time estimated with premature stimulation and spontaneous cycle length.[16] Furthermore, it did not correlate with corrected sinus nodal recovery time when the atrium was paced at the shortest possible cycle length. Correlation was better between sinoatrial conduction time estimated with continuous atrial pacing and sinus nodal recovery time at a pacing cycle length that was 60 msec shorter. This finding suggests that under these circumstances the effects of continuous atrial pacing on

the sinus mode were similar to those of high rate atrial pacing.

Validity of premature and continuous atrial stimulation methods: The most important question arising from our data is which approach gives the correct results. From experimental studies it is well known that sinoatrial conduction time estimated with the premature stimulus technique may differ from true sinoatrial conduction time to a varying degree.[22] To date, no similar comparative experimental studies have been performed using the continuous atrial pacing technique. Therefore, the validity of the techniques cannot be assessed from our study.

The fact that the first cycles after continuous atrial pacing are often longer than the spontaneous cycle length, as shown in our study, suggests some overdrive effect on sinus nodal automaticity. Conversely, premature discharge of the sinus node may also have a depressant effect on sinus nodal automaticity.[15,23,26,37] The greater length in the majority of cases of sinoatrial conduction time estimated with premature stimulation than of that estimates with continuous pacing suggests that the depressing effect of both procedures on sinus nodal automaticity may be more pronounced with premature stimulation than with continuous atrial pacing.

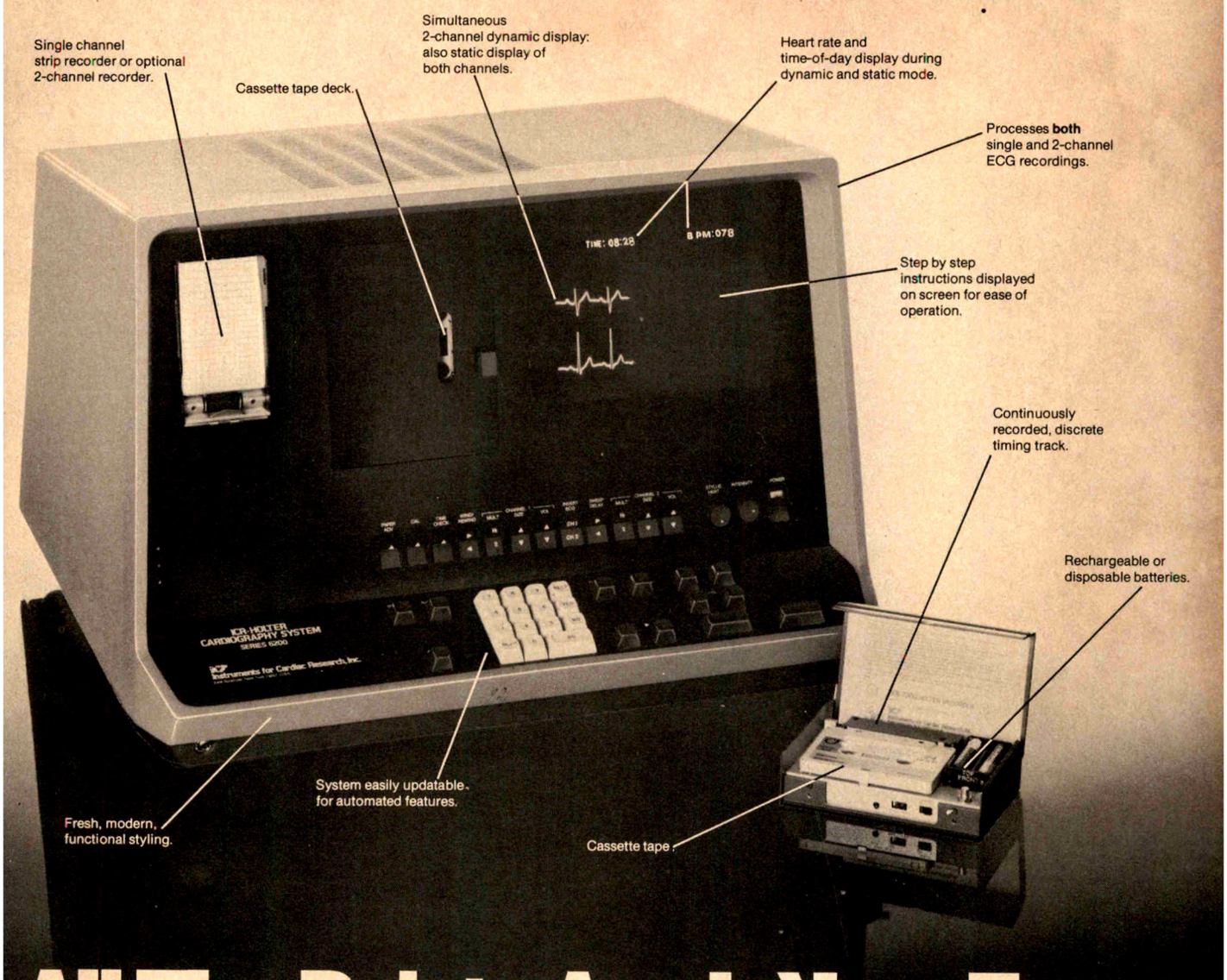
Implications: Our study suggests that we will not know which method of estimating sinoatrial conduction time is correct until the problems encountered have been studied experimentally. Because the results of the two techniques differ so greatly the range of normal for the continuous atrial pacing technique has to be delineated before the method can be used to evaluate patients with sinus nodal dysfunction. However, the continuous pacing technique, if found valid, will allow essentially all catheterization laboratories to obtain measurements of sinoatrial conduction time because no special stimulator is needed.

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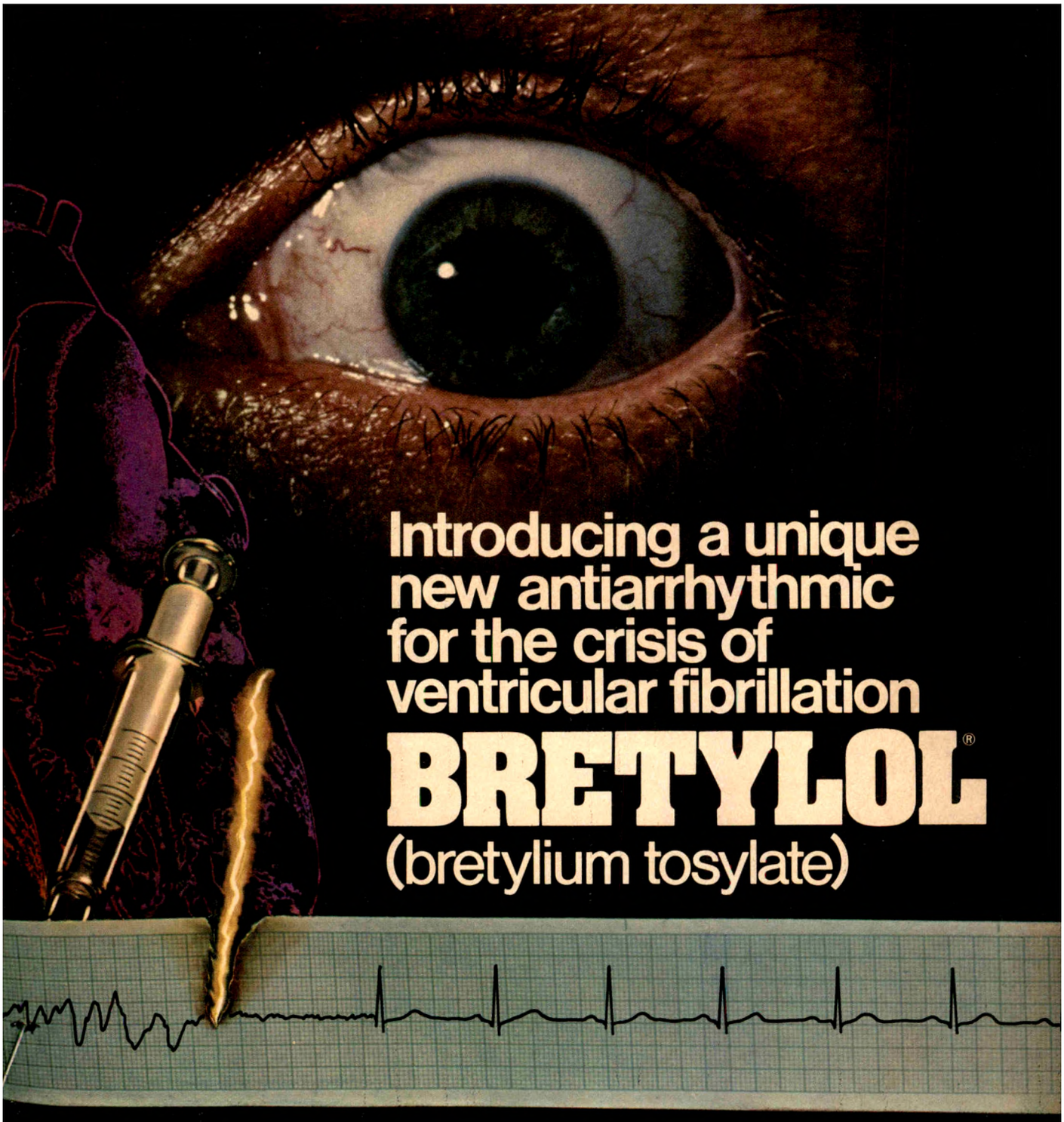
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Introducing a unique new antiarrhythmic for the crisis of ventricular fibrillation

BRETYLOL®

(bretylium tosylate)

Not meant to imply time relationship between administration of Bretylol and patient response.

BRETYLOL® (bretylium tosylate) is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to first-line therapy.

BRETYLOL® bretylium tosylate

At present, Bretylol should not be considered a first-line antiarrhythmic agent. Use of Bretylol should be limited to facilities where equipment for constant monitoring of arrhythmias is available.

BRETYLOL: in ventricular fibrillation

In reported clinical situations, BRETYLOL® (bretylium tosylate) was effective in conjunction with electrical cardioversion, even in patients refractory to other antiarrhythmic therapies. BRETYLOL raised the ventricular fibrillation threshold in animal studies. Suppression of ventricular fibrillation usually occurs within minutes following intravenous administration, the effect generally lasting 6 to 8 hours.

BRETYLOL: in ventricular tachycardia

In clinical studies, BRETYLOL was effective in the management of ventricular tachycardia and other ventricular ectopic rhythms, even those recurrent and refractory to existing antiarrhythmic therapies. Clinical benefits can usually be observed 20 minutes or more following parenteral administration with duration of action 6 to 8 hours.

BRETYLOL: effects on cardiac function

Unlike other antiarrhythmic drugs, BRETYLOL has demonstrated (in animal studies) a positive inotropic effect on the myocardium and did not significantly decrease A-V conductivity. In man, BRETYLOL generally did not depress myocardial function and maintained cardiac output. These effects may be due to release of norepinephrine from nerve terminals, potentiation of the effects of endogenous catecholamines and/or a direct action on the myocardium.

BRETYLOL: contraindications/adverse reactions

There are no contraindications for BRETYLOL in the treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

The principal adverse reaction is hypotension, usually postural. This is due to reduction of peripheral vascular sympathetic tone, *not* to depression of myocardial function.

Due to the initial release of norepinephrine from the adrenergic postganglionic terminals, there may be initial *transient* increases in blood pressure, heart rate and/or PVC's. These generally return promptly to preadministration levels.

Nausea and vomiting can usually be obviated by the slow intravenous administration of a dilute solution of BRETYLOL.

For a full description of adverse reactions, please refer to the complete prescribing information on the last page of this advertisement.

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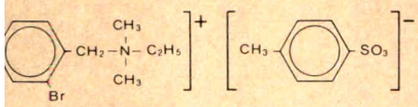
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RETYLOL INJECTION

R INTRAMUSCULAR OR INTRAVENOUS USE

SCRIPTION

TYLOL (bretylium tosylate) is o-Bromobenzyl ethyldimethylammonium luene sulfonate. The chemical structure is:



$H_{24}BrNO_3S$ Mol. Wt. 414.39

TYLOL is a white, crystalline powder with an extremely bitter taste. It is ly soluble in water and alcohol. Each ml of sterile, pyrogen-free solution tains 50 mg bretylium tosylate in Water for Injection, USP. The pH is usted, when necessary, with dilute hydrochloric acid or sodium hydroxide. TYLOL contains no preservative.

NICAL PHARMACOLOGY

TYLOL (bretylium tosylate) is a bromobenzyl quaternary ammonium com- nd which selectively accumulates in sympathetic ganglia and their post- glionic adrenergic neurons where it inhibits norepinephrine release by ressing adrenergic nerve terminal excitability.

RETYLOL also suppresses ventricular fibrillation and ventricular ar- hmias. The mechanisms of the antifibrillatory and antiarrhythmic actions RETYLOL are not established. In efforts to define these mechanisms, following electrophysiologic actions of BRETYLOL have been demon- ted in animal experiments:

ncrease in ventricular fibrillation threshold.

ncrease in action potential duration and effective refractory period without nges in heart rate.

ittle effect on the rate of rise or amplitude of the cardiac action potential se 0) or in resting membrane potential (Phase 4) in normal myocardium. wever, when cell injury slows the rate of rise, decreases amplitude, and ers resting membrane potential, BRETYLOL restores these parameters ard normal.

ncrease in impulse formation and spontaneous firing rate of pacemaker ue as well as increased ventricular induction velocity.

restoration of injured myocardial cell electrophysiology toward normal,

(Prescribing Information continued below)

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

(Prescribing Information continued below)

ular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. Since there is a delay in onset of its antiarrhythmic action, BRETYLOL is not to be considered or used as a replacement for rapidly-acting antiarrhythmic agents currently in use. The clinical use of BRETYLOL is for short-term use only. Patients should either be kept supine during the course of BRETYLOL therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of BRETYLOL has not been determined. There is comparatively little experience with dosages greater than 30 mg/kg/day, although such doses have been used without apparent adverse effects. The following schedule is suggested:

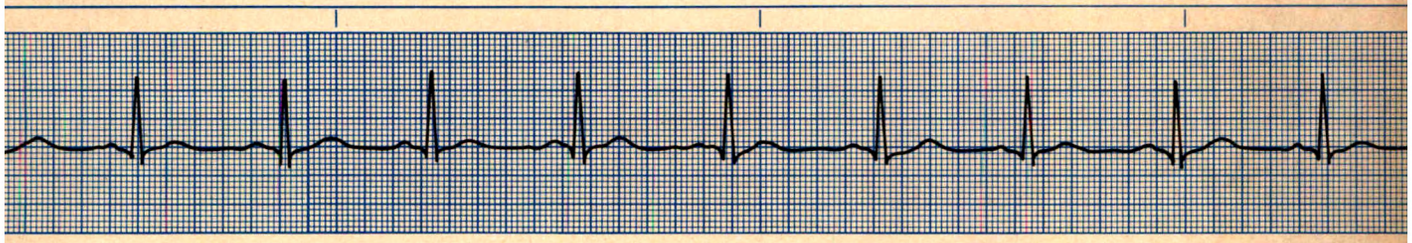
A. For Immediately Life-threatening Ventricular Arrhythmia, as in Ventricular Fibrillation: Administer undiluted BRETYLOL at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated at 15 to 30 minute intervals until a total dose of not more than 30 mg/kg of body weight has been given. For maintenance dosage, see below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as follows before intravenous administration:* Using aseptic technique, dilute contents of one BRETYLOL ampul (10 ml containing 500 mg bretylium tosylate) to a minimum of 50 ml with Dextrose Injection, USP or Sodium Chloride Injection, USP.

Administer the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg of body weight by intravenous infusion over a period greater than 8 min-

(Prescribing Information continued below)



ell as the increase of the action potential duration and effective refractory od without changing their ratio to each other, may be important factors in pressing re-entry of aberrant impulses and decreasing induced dispersion cal excitable states.

RETYLOL induces a chemical sympathectomy-like state which resem- a surgical sympathectomy. Catecholamine stores are not depleted by TYLOL, but catecholamine effects on the myocardium and on peripheral ular resistance are often seen shortly after administration because TYLOL causes an early release of norepinephrine from the adrenergic ganglionic nerve terminals. Subsequently, BRETYLOL blocks the re- e of norepinephrine in response to neuron stimulation. Peripheral ad- rgic blockade regularly causes orthostatic hypotension but has less ct on supine blood pressure. The relationship of adrenergic blockade to antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a y in patients with frequent ventricular premature beats, peak plasma centration of BRETYLOL and peak hypotensive effects were seen within hour of intramuscular administration, presumably reflecting adrenergic onal blockade. However, suppression of premature ventricular beats was maximal until 6-9 hours after dosing, when mean plasma concentration declined to less than one-half of peak level. This suggests a slower hanism, other than neuronal blockade, was involved in suppression of rrhythmia. On the other hand, antifibrillatory effects can be seen within tes of an intravenous injection, suggesting that the effect on the cardium may occur quite rapidly.

RETYLOL has a positive inotropic effect on the myocardium, but it is yet certain whether this effect is direct or is mediated by catecholamine se.

RETYLOL is eliminated intact by the kidneys. No metabolites have been tified following administration of BRETYLOL in man and laboratory ani- . In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose creted in the urine during the first 24 hours, with an additional 10% eted over the next three days.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventric-

utes. More rapid infusion may cause nausea and vomiting. A second dose may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: (*Do not dilute BRETYLOL prior to intramuscular injection.*) Inject 5 to 10 mg BRETYLOL per kg of body weight. Dosage may be repeated in 1 to 2 hours if the arrhythmia persists. Thereafter maintain with same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and the site of injection should be varied on repeated injection.

C. Maintenance Dosage: The diluted BRETYLOL solution may be administered by intermittent bolus infusion or by constant infusion.

1. Intermittent Infusion: Infuse the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion may cause nausea and vomiting.

2. Constant Infusion: Infuse the diluted solution at a dosage of 1 to 2 mg BRETYLOL per minute.

Dosage of BRETYLOL should be reduced and discontinued in 3 to 5 days under electrocardiographic monitoring. Other appropriate antiarrhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP. pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, pyrogen-free. July 1978

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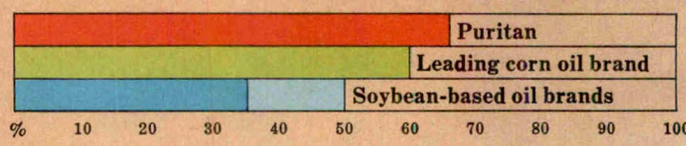
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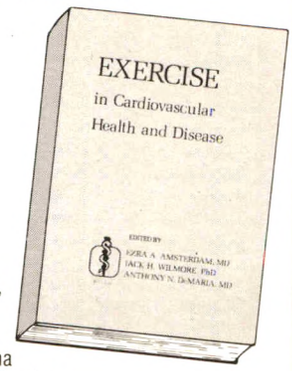


The nutrition department of a major university has published the results of a study[1] that evaluated a dietary serum-cholesterol-reducing program which included Puritan Oil. The study was conducted in a family situation—entire families used Puritan as part of a total serum-cholesterol-reducing diet. The data showed significant decreases in serum cholesterol levels among all participating groups. These lowered levels were reached within 10 days, and were maintained throughout the diet modification period.

Reference: 1. Witchi, J.C. et al., *J. Am. Dietetic Assoc. 72:* 384, 1978.

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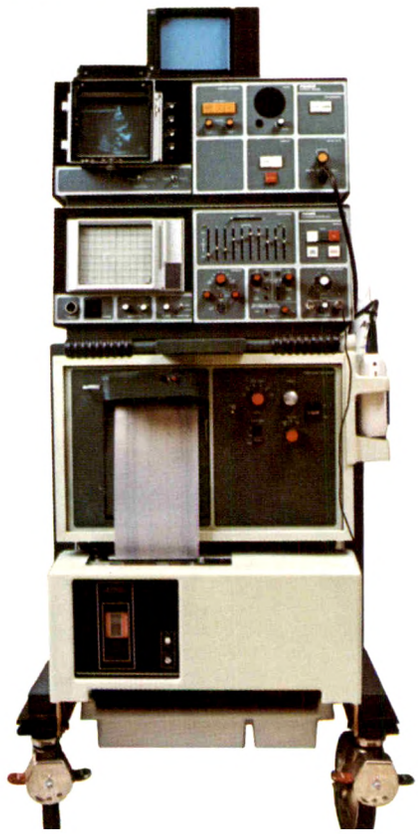
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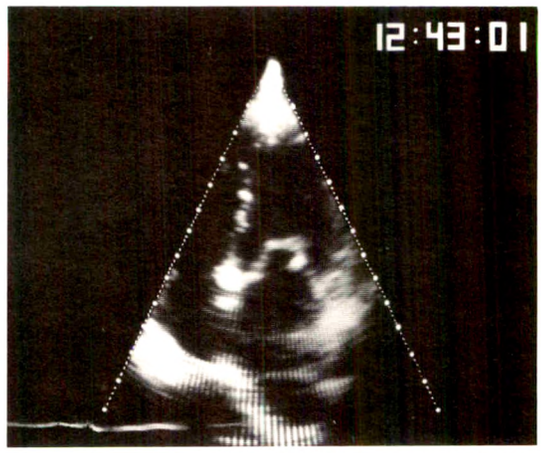
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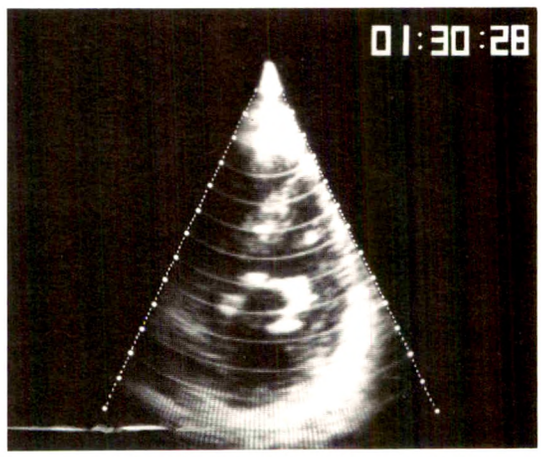
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MITRAL STENOSIS 48 yr. old male. Hemiaxial view from the apex.

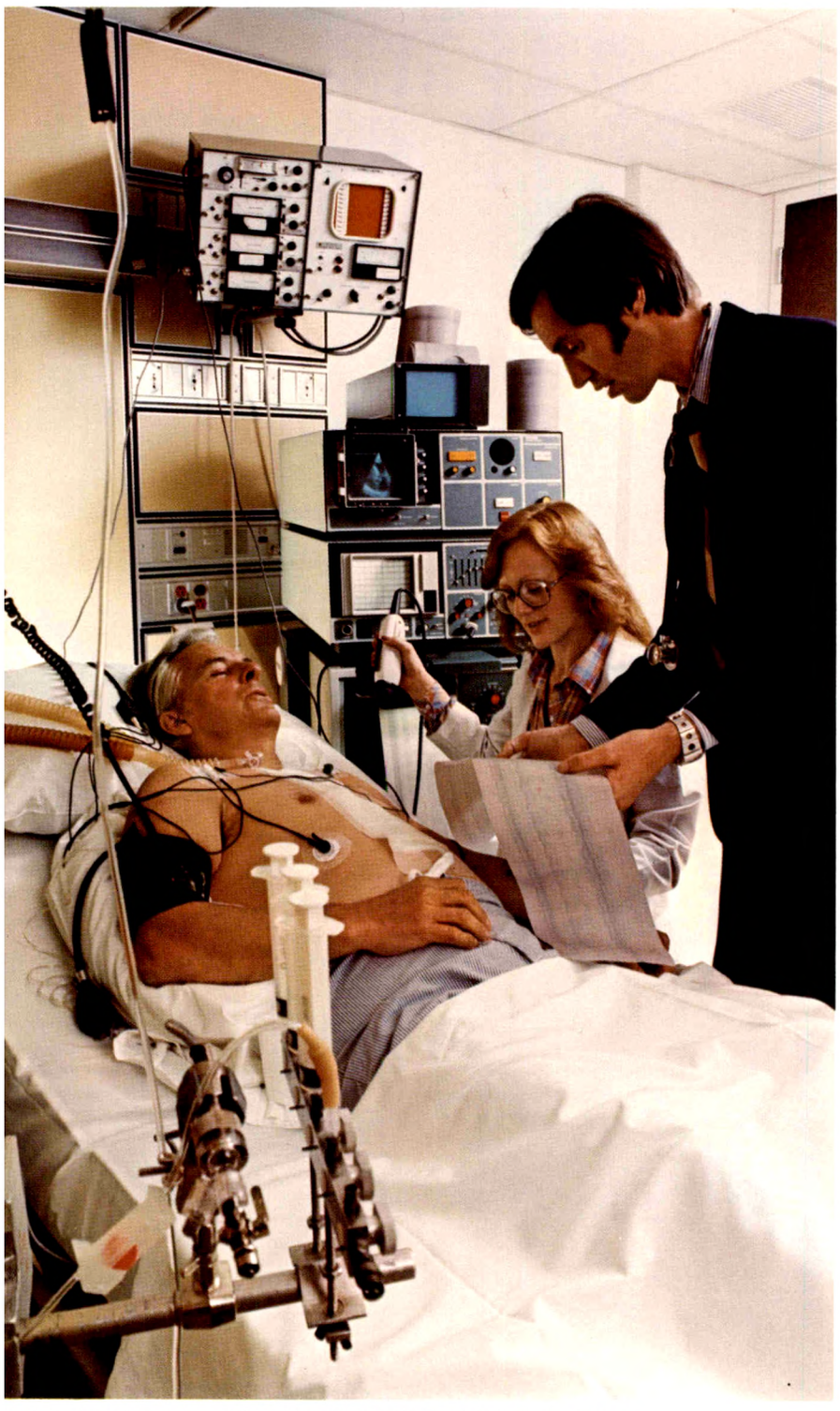


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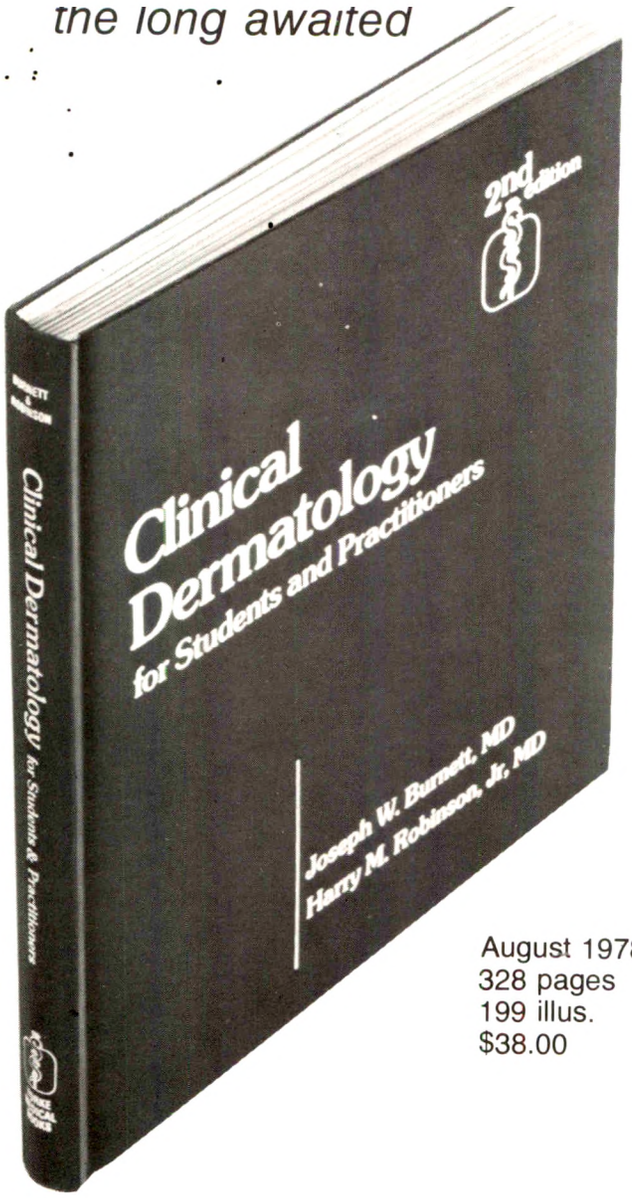
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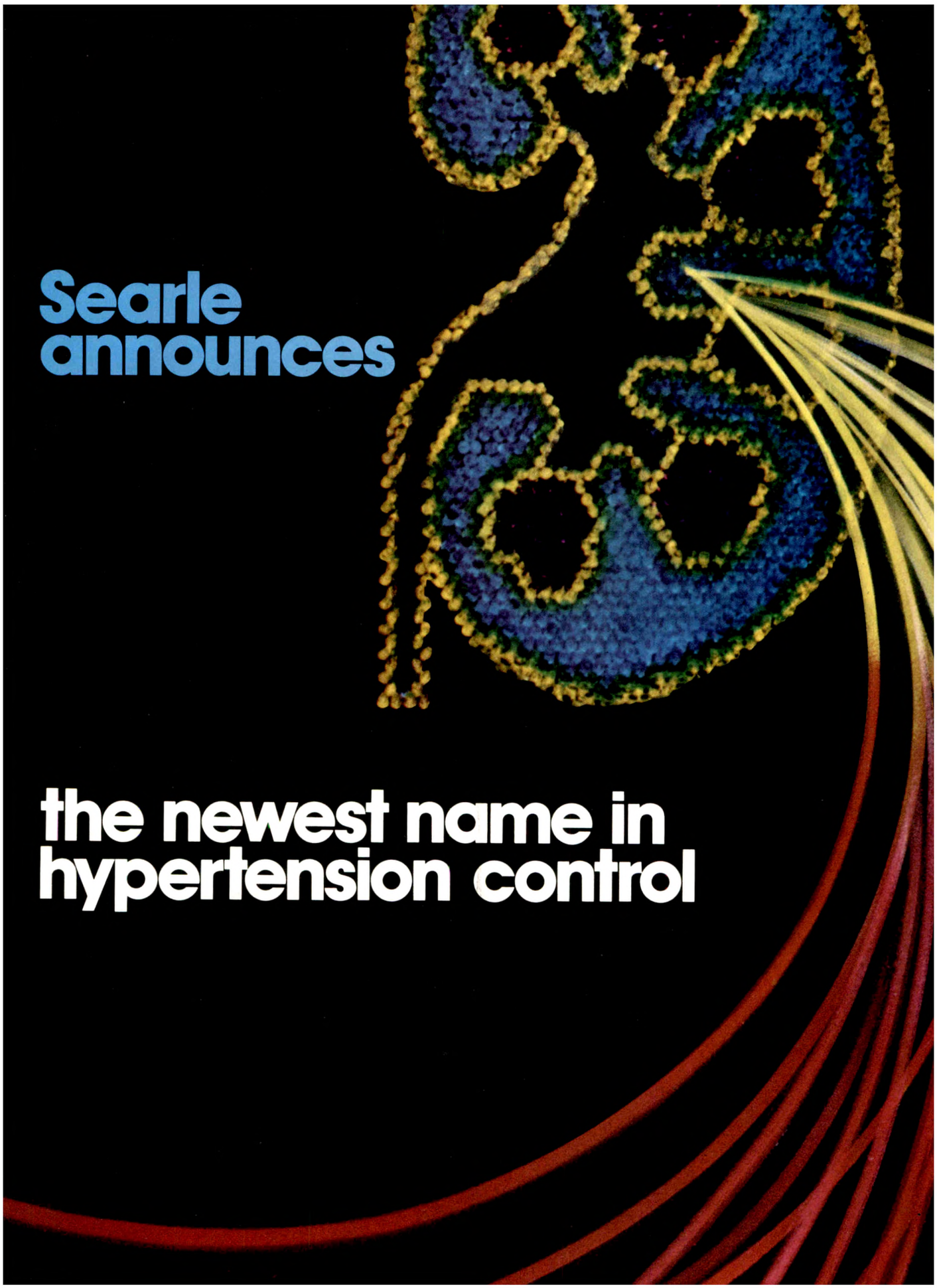
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- a duration of action that provides 24-hour hypertension control with a single tablet daily
- peak diuretic activity during waking hours...low potential for nocturia
- three tablet strengths for dosage flexibility
- easily accomplished dosage titration
- effective in patients with low GFR ...because of its dual renal tubular action

SEARLE

Please see last page for a brief summary

Not just another thiazide

Diulo (metolazone) is a thiazide-like diuretic – the latest in a progression of products that began with chlorothiazide in 1957, and led to the introduction of furosemide nearly a decade later.

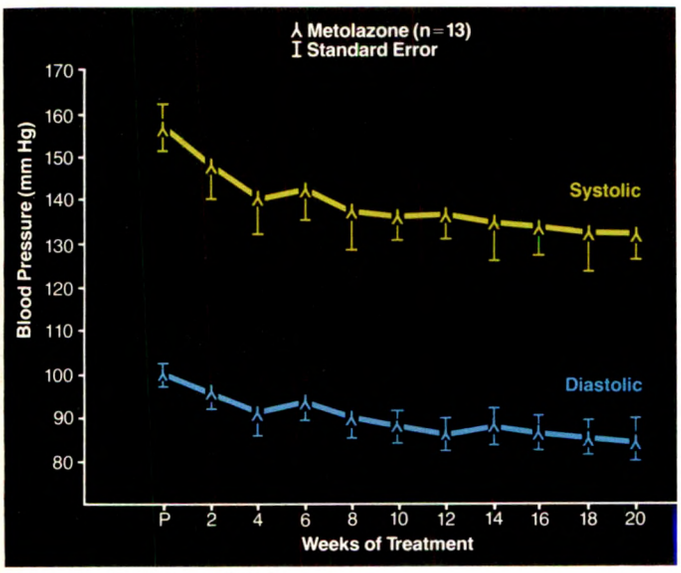
In Diulo, however, is found a different molecular structure, one which distinguishes it pharmacologically and clinically from the thiazides, as well as from the osmotic agents, carbonic anhydrase inhibitors, loop of Henle blockers, mercurials and potassium-sparing diuretics.

Furthermore, Diulo offers a combination of exceptional features and benefits that make it the distinctive Step 1 diuretic for hypertension.

As effective and well tolerated as any thiazide or thiazide-like diuretic

In extensive clinical trials[1-8] excellent results were obtained with metolazone in blood pressure reduction and the incidence of annoying side effects was low. Metolazone has been described as superior in efficacy to hydrochlorothiazide[1] and more active on a milligram basis.[1,2] Another clinical trial[3] has shown metolazone to be as effective as chlorthalidone. Results presented in the accompanying graph are typical of those obtained in extensive clinical trials.

Blood pressure changes over a 20-week period in patients completing an initial treatment interval with metolazone.



(Adapted from Van Hoose and Cutler[7])

Additionally, the active ingredient of Diulo has been cited[2,5-8] for the low incidence of untoward reactions associated with its use. Side effects encountered are those generally observed with the thiazides, such as gastrointestinal symptoms, drowsiness and symptoms related to volume depletion.

In the experience of one investigator, "...muscle weakness, tiredness, and dry mouth...have seldom been a problem with this drug [metolazone]."[8]

Once-a-day dosage regimen to encourage patient compliance

"Metolazone can also simplify dosage schedules... since it is effective in single daily doses."[2]

With Diulo diuresis usually begins within one hour, with maximum diuresis occurring in about two hours. As a result of the drug's pharmacokinetics, diuretic effect persists up to 24 hours. You can thus maintain antihypertensive control for a 24-hour period.

For these reasons, Diulo provides for a "one tablet each morning" regimen. In the experience of several teams of investigators,[2,6-8] this advantage contributes to patient compliance.

A duration of action that provides 24-hour hypertension control with a single tablet daily

The characteristic absorption and distribution of metolazone in the body can help to explain some of the important therapeutic features and benefits of Diulo. Because it binds to plasma protein and is excreted relatively slowly, Diulo has a prolonged duration of action and maintains round-the-clock control of blood pressure with one tablet in the morning. Compatible with the average patient's life-style, it is taken at the start of the routine day. Activity of the drug parallels, rather than intrudes upon, the busy hours spent at work, the quieter mealtime hour and the more relaxed evening hours. At the usual antihypertensive dose, blood pressure control is provided for 24 hours.

Peak diuretic activity during waking hours... low potential for nocturia

The requisite daily single dose of Diulo exerts maximum diuresis in about two hours and the major part of its diuretic action takes place during the first 16 hours after administration. In preintroductory studies[9] involving 1,612 patients, only 11 or 0.682% of patients reported nocturia.

Three tablet strengths for dosage flexibility

Diulo is supplied in three tablet strengths, and each can be administered on a once-daily basis. Clinicians are thus afforded latitude in individualizing therapy according to patient response, while maintaining an easily-complied-with, one-tablet-daily dosage regimen ... a notable combination of dosage flexibility and patient convenience.

Easily accomplished dosage titration

Prudence suggests that in programs of hypertension management, drugs should be administered in sufficient dosage to gain a maximal initial therapeutic response, but in the smallest dosage possible to maintain that therapeutic response.

If the regimen of a particular diuretic calls for tablets to be broken in half, or taken in various combinations or sequences, it may be difficult to titrate dosage without compromising the compliance advantage of one-tablet-a-day therapy.

Diulo with its three dosage strengths of 2½, 5 and 10 mg. permits easy adjustment of intake and titration flexibility... while the patient continues to take just one tablet a day.

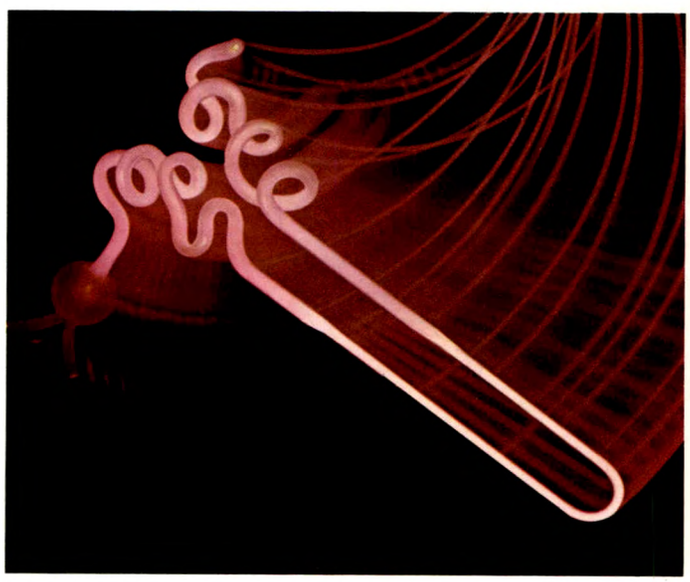
Effective in patients with low glomerular filtration rate (GFR)... because of its dual renal tubular action

Diulo exerts action at *two* renal tubular sites – distally as well as at a proximal site. It acts primarily by inhibiting sodium reabsorption in the cortical diluting segment, and secondarily blocks reabsorption in the proximal tubule. Unlike the thiazides and chlorthalidone, Diulo accomplishes this secondary action without interfering with carbonic anhydrase. This duality of effect is important when one considers the propensity of the thiazides to reduce GFR and, often, renal plasma flow (RPF).

During a study[10] designed to evaluate metolazone in 17 patients with chronically depressed GFR and in three with nephrotic syndrome, significant blood pressure reduction, adequate diuresis or both, were attained by 80% of the patients.

Diulo can thus be recommended not only for those with uncomplicated hypertension, but also when the hypertension is complicated by renal problems – a clear-cut therapeutic advantage unattainable with thiazides or chlorthalidone.

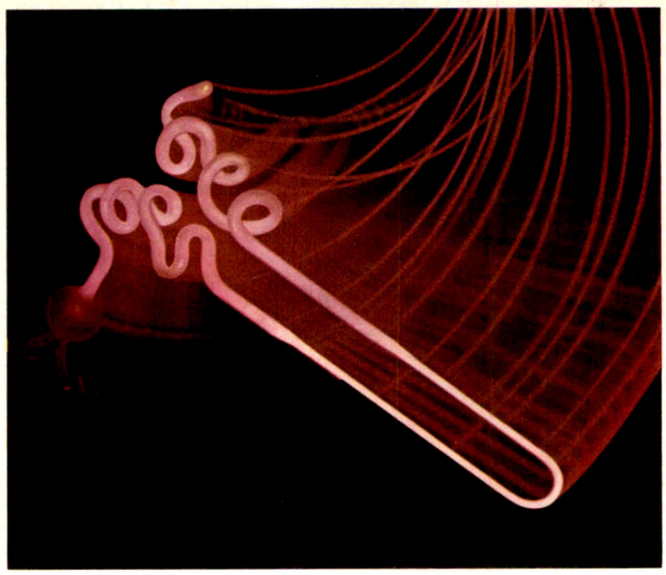
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DIULO™

(METOLAZONE)



DIULO™ (metolazone) 2½-mg., 5-mg. and 10-mg. tablets Before prescribing, see complete prescribing information. The following is a brief summary: **Indications:** Diulo (metolazone) is an antihypertensive diuretic indicated for the management of mild to moderate essential hypertension as sole therapeutic agent and in the more severe forms of hypertension in conjunction with other antihypertensive agents. Also, edema associated with heart failure and renal disease. **Contraindications:** Anuria, hepatic coma or precoma; allergy or sensitivity to metolazone. **Warnings:** In theory, cross-allergy may occur in patients allergic to sulfonamide-derived drugs, thiazides or quinethazone. Hypokalemia may occur, and is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may occur. Azotemia and hyperuricemia may be noted or precipitated. Considerable potentiation may occur when given concurrently with furosemide. When added to other antihypertensives, the dosage of the other agents should be reduced. Use with potassium-sparing diuretics may cause potassium retention and hyperkalemia. Administration to pregnant women or those of childbearing age requires that potential benefits be weighed against possible hazards to the fetus. Metolazone appears in the breast milk. Not recommended for pediatric use. **Precautions:** Perform periodic examination of serum electrolytes, BUN, uric acid, and glucose. Observe patients for signs of fluid or electrolyte imbalance, hyponatremia, hypochloremic alkalosis and hypokalemia. These determinations are particularly important when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur. **Adverse Reactions:** Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks. **Usual Initial Once-Daily Dosages:** Mild to moderate essential hypertension — 2½ to 5 mg.; edema of cardiac failure — 5 to 10 mg.; edema of renal disease — 5 to 20 mg. Dosage adjustment is usually necessary during the course of therapy. **How Supplied:** Tablets, 2½, 5 and 10 mg.; in bottles of 100.

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Right Atrial Ultrastructure in Congenital Heart Disease. I. Comparison of Ventricular Septal Defect and Endocardial Cushion Defect

TUAN DUC PHAM, PhD
ANDREW L. WIT, PhD*
ALLAN J. HORDOF, MD
JAMES R. MALM, MD, FACC
JOHN J. FENOGLIO, Jr., MD, FACC†

New York, New York

Ultrastructural studies were performed on portions of the operatively resected right atrium from six patients with a ventricular septal defect and six patients with an endocardial cushion defect. The six patients with a ventricular septal defect had normal right atrial mean pressure and no evidence of right atrial volume overload. Ultrastructurally, the atrial muscle cells in these patients appeared normal and measured 6 to 12 μ in diameter. The six patients with an endocardial cushion defect had elevated right atrial mean pressure and evidence of right atrial volume overload. Ultrastructurally, the atrial muscle cells in these patients were generally larger than 12 μ in diameter. The cells were irregular and had multiple and occasionally widened intercalated discs. In addition, there were degenerative changes in two patients with markedly increased atrial pressure. These changes included extensive loss of contractile elements, aggregation of small irregular mitochondria and proliferation of tubules of the sarcoplasmic reticulum. The structural changes suggest that hypertrophy of the right atrium may be secondary to volume overload of the atrium, whereas degenerative changes may be secondary to increased right atrial pressure.

Cardiac disease may cause changes in cardiac ultrastructure that may have functional consequences. For example, increases in connective tissue associated with hypertrophy may decrease ventricular compliance,[1] alterations in myocardial structure associated with ventricular hypoxia may affect contractility[2] and changes in intercell junctions in the sinus node may influence impulse initiation and conduction.[3] There are a number of detailed studies on the ultrastructural changes of the ventricular myocardium in both congenital[4] and acquired disease.[5–7] However, atrial ultrastructure has only been characterized in detail in chronic rheumatic heart disease.[8] Other studies of human atrial ultrastructure have been of limited scope.[9–19]

We have begun to determine the effects of congenital heart disease on atrial ultrastructure. In congenital heart disease, the atrial myocardium is not primarily affected by a disease process. Any changes in atrial structure present in patients with congenital heart disease might be the result of hemodynamic alterations such as atrial pressure or volume overload caused by the malformation of the heart. To determine whether such structural changes occur and whether they are related to hemodynamic alterations were the goals of this study. We compared the ultrastructure of right atrial tissue from patients with an uncomplicated ventricular septal defect and normal atrial hemodynamics with the ultrastructure of right atrial tissue from patients with an endocardial cushion defect and significantly elevated right atrial pressure and volume. We found marked changes in the structure of the right atrium of

From the Departments of Pathology, Pediatrics, Pharmacology and Surgery, College of Physicians and Surgeons, Columbia University, New York, New York. This study was supported by Grant HL-12738 from the U. S. Public Health Service, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received April 3, 1978; revised manuscript received July 5, 1978, accepted July 5, 1978.

* Career Scientist of the Irma T. Hirschl Trust, New York, New York.

† Recipient of Career Development Award 1-K04-HL00185, from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: John J. Fenoglio, Jr., MD, Department of Pathology, College of Physicians and Surgeons, Columbia University, 630 West 168 Street, New York, New York 10032.

TABLE I

Clinical Data in Six Patients With a Ventricular Septal Defect and Six Patients With Endocardial Cushion Defect

Case no.	Age	Sex	Right Atrial Pressure (mm Hg)			Qp/Qs Ratio	Atrial Size*
			A Wave	*V* Wave	Mean		
			A. Patients With a Ventricular Septal Defect				
1	6 wk	F	3	3	3	2.1:1	1+
2	3 mo	M	6	2	2	2:1	1+
3	15 mo	M	4	4	2	5:1	1+
4	18 mo	F	5	5	3	2.7:1	1+
5	3 1/2 yr	F	4	3	2	1.8:1	1+
6	5 1/2 yr	M	5	2	1	2:1	1+
			B. Patients With an Endocardial Cushion Defect				
7	19 mo	F	7	6	5	2.5:1	4+
8	20 mo	M	8	3	5	1.75:1	4+
9	5 yr	F	15	10	8	1.5:1	4+
10†	5 yr	M	5	3	3	1:1	4+
11	6 yr	M	16	12	10	4.3:1	4+
12	12 yr	M	12	8	6	1.5:1	4+

* As assessed at the time of operation: 1+ = near normal size; 2+ = mild dilatation; 3+ = moderate dilatation; 4+ = marked dilatation.
† This patient's pulmonary artery was banded at age 5 months.
Qp/Qs ratio = ratio of pulmonary to systemic blood flow.

patients with an endocardial cushion defect. These changes appear to be related to the hemodynamic alterations in these patients and may have important functional consequences. In the course of the study we also found that the structure of the atrium of patients with a ventricular septal defect was identical with that of normal atria in animals[20] and was, therefore, presumably normal. As a result we were able to characterize normal human atrial ultrastructure in detail.

Material and Methods

Patients studied: Tissue for this study was obtained at the time of open heart surgery in 12 patients with congenital heart disease. Six patients had an uncomplicated ventricular septal defect, and six had an endocardial cushion defect (Table I).

The six patients with a ventricular septal defect ranged in age from 6 weeks to 5 1/2 years. Right atrial mean pressure was normal (less than 5 mm Hg) and a left to right shunt was demonstrated across the ventricular septum in each patient. Right atrial blood flow was assumed to be normal. Pulmonary arterial pressure ranged from 33 to 58 mm Hg in the six patients. However, there was no evidence of decreased right

TABLE II

Ultrastructural Changes in Six Patients With a Ventricular Septal Defect and Six Patients With an Endocardial Cushion Defect

Case no.	Z Bands*	Intercalated Discs†	Degenerative Changes‡
	A. Patients With a Ventricular Septal Defect		
1	0	0	0
2	0	0	0
3	0	0	0
4	+	0	0
5	+	0	0
6	0	0	0
	B. Patients With an Endocardial Cushion Defect		
7	+++	+	0
8	+++	+	0
9	++++	++	++
10	++	0	0
11	++++	++	++
12	++++	++	0

Z band changes include both thickening of Z bands and abnormal accumulations of Z band-like material.
† Intercalated disc changes include increased fibrillar material and irregularity and widening of discs.
‡ Degenerative changes include loss of myofilaments, aggregation of mitochondria and condensation of sarcoplasmic reticulum.
0 = not present; + = present in less than 1 percent of cells; ++ = present in 1 to 5 percent of cells; +++ = present in 5 to 10 percent of cells; ++++ = present in 10 percent or more of cells.

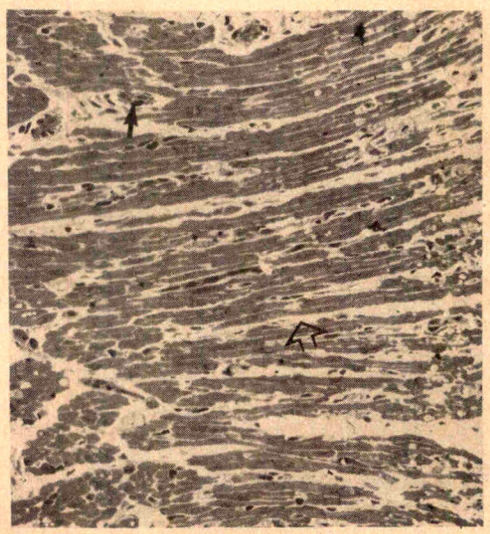


FIGURE 1. Case 2. Portion of the right atrial free wall from the heart of a patient with a ventricular septal defect. By light microscopy the atrial cells are of normal size and arranged in parallel. Interstitial connective tissue is scant (**open arrow**) and the small blood vessels are normal (**solid arrow**). (Toluidine blue ×208, reduced by 23 percent.)

ventricular compliance as evidenced by the normal right atrial pressure. Atrial size was assessed visually at the time of surgery and was judged to be normal or only slightly dilated.

The six patients with an endocardial cushion defect ranged in age from 19 months to 12 years. Catheterization before surgery demonstrated a complete atrioventricular canal in each patient. Mean right atrial pressure was elevated (greater than 5 mm Hg) and a left to right shunt was documented in all but one patient. The atrium was judged to be markedly dilated at the time of surgery in all patients. The left to right shunt was assumed to have resulted in increased right atrial blood flow because of its anatomic location in patients with an endocardial cushion defect. In Patient 10 (Table I) the pulmonary artery had been banded at age 5 months and, although the right atrium was greatly dilated, the mean right atrial pressure was normal and a left to right shunt was not documented.

Tissue preparation: The right atrial tissue was obtained adjacent to the atriotomy site on the anterior wall in all 12 patients. The tissue was either cut into 1 to 2 mm blocks and fixed immediately in 2.5 percent phosphate buffered (pH 7.3) glutaraldehyde in the operating room or first superfused in Tyrode's solution in a tissue bath while transmembrane action potentials were recorded.[21,22] Previous work in this laboratory[23] has shown that superfusion in Tyrode's solution has no effect on the ultrastructure of the first 8 to 10 cell layers beneath the endocardial surface. After the in vitro electrophysiologic studies the tissue was cut into small blocks and fixed in 2.5 percent glutaraldehyde. All tissue was fixed a minimum of 4 hours and usually overnight in glutaraldehyde. Post-fixation was carried out for 1 hour in chilled 1 percent phosphate buffered (pH 7.4) osmium oxide, after which the tissue was dehydrated in graded acetones and embedded in Swiss araldite. The tissue was embedded in flat embedding molds to preserve the orientation of muscle cells to the endocardium.[23]

Thick sections (1 μ) were cut from 6 to 10 tissue blocks in each patient and stained with 1 percent toluidine blue. Ultrathin sections were cut with a Sorvall MT2 ultramicrotone, stained with uranyl acetate and lead citrate[24] and examined with a Philips 300 electron microscope at 80 kv. The tissues prepared as described were with few exceptions well preserved.

The incidence of ultrastructural changes in atrial cells of patients with ventricular septal defect and endocardial cushion defect was evaluated. Low power electron micrographs (×3,000) were taken from each grid, and the number of cells in the thin section was counted. At least eight grids and approximately 200 cells were studied in each patient. The cells with ultrastructural changes were counted, and an approximate incidence of each ultrastructural change calculated. The extent of the changes in each patient was then graded on a scale of 1 to 4 (Table II).

Results

Right Atrial Structure in Ventricular Septal Defect

Cell size and interstitium: The muscle cells were orderly arranged and of normal size, measuring 6 to 12 μ in diameter at the level of the nucleus. The interstitial and subendocardial connective tissue appeared normal (Fig. 1). The blood vessels were normal and there was no evidence of perivascular fibrosis. Nerves were present and appeared structurally normal.

Sarcolemma and specialized junctions: The cells were invested by a basement membrane, approximately 300 Å thick, composed of fine filamentous material (Fig. 2). The

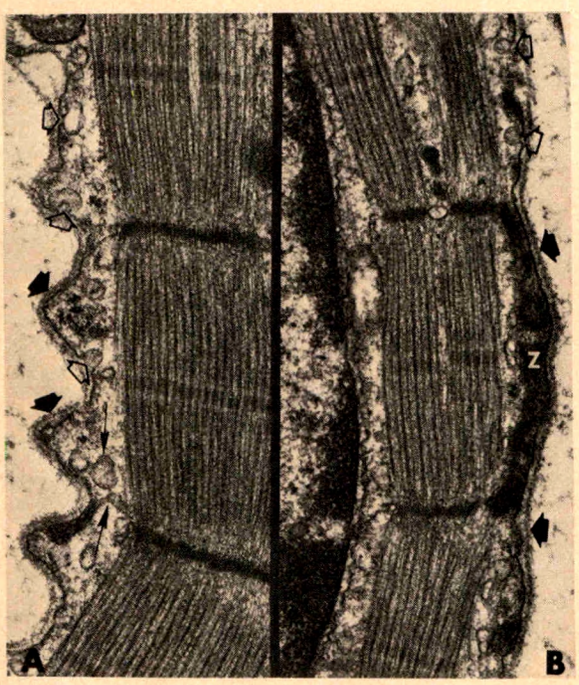


FIGURE 2. Case 2. Normal-appearing right atrial cells from the heart of a patient with a ventricular septal defect. The sarcolemma is invested by a basement membrane approximately 300 Å thick (**solid arrows**). Beneath the sarcolemma rows of pinocytic vesicles (**open arrows**) and tubules of the sarcoplasmic reticulum (**small arrows**) are conspicuous. Occasionally (**B**) deposits of Z band-like material (Z) are present just beneath the sarcolemma. (**A** and **B** ×34,400, reduced by 23 percent.)

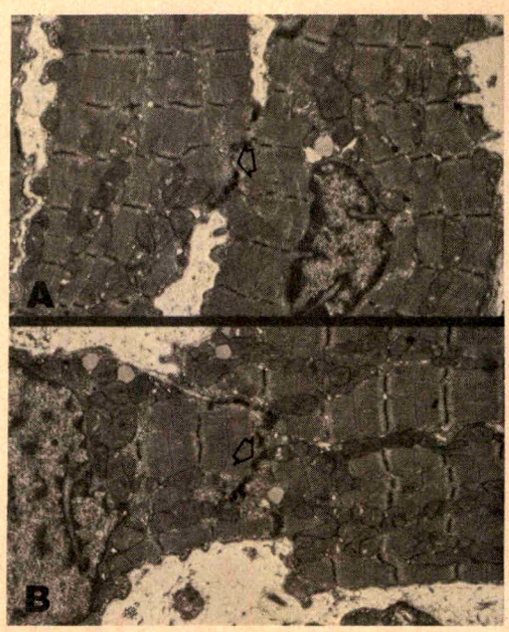


FIGURE 3. Case 2. Well developed intact intercalated discs between atrial cells from the heart of a patient with a ventricular septal defect. Both end to end (**A**) and side to side (**B**) junctions (**arrows**) are present. (**A** and **B** ×5,950, reduced by 23 percent.)

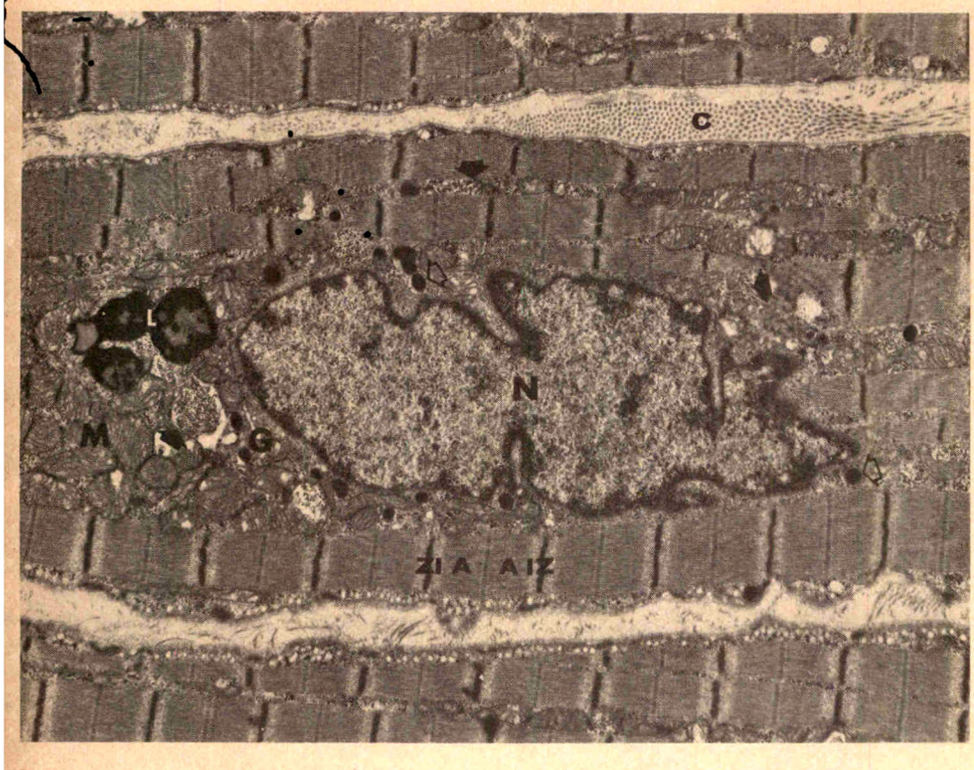


FIGURE 4. Case 6. The right atrial cells from the heart of this patient with a ventricular septal defect resemble those of a normal cat. The sarcomeres are in register across the cell, and distinct A bands (A), I bands (I) and Z bands (Z) are discernible. The nucleus (N) is centrally located, and accumulations of mitochondria (M) and glycogen (**solid arrows**) are prominent in the perinuclear region. Atrial-specific granules (**open arrows**) are prominent, and electron-dense bodies (L) are occasionally encountered. Profiles of the Golgi apparatus (G) are present adjacent to the nucleus. Abundant collagen fibers (c) are present in the interstitial space. (×12,900, reduced by 23 percent.)

basement membrane was separated from the sarcolemma by an irregular space that ranged from 300 to 400 Å in thickness. Rows of pinocytotic vesicles were frequently present on the inner aspect of the sarcolemma. We did not see invaginations of the sarcolemma forming T tubules even though T tubules have been reported to be occasionally present in normal atrial cells especially in the pectinate muscles of the right atrium.[14,20] Portions of the sarcoplasmic reticulum system were often in close apposition to the sarcolemma. Deposits of Z band-like material (Fig. 2B) were present along the inner aspect of the sarcolemma in less than 1 percent of the cells in all patients.

Specialized portions of the cell membrane at cell junctions were well developed, and both side to side (Fig. 3A) and end to end intercalated discs (Fig. 3B) were frequent. The intercalated discs consisted of fascia adherens, macular adherens, macular occludens (nexuses) and undifferentiated portions. In many areas myofilaments appeared to be anchored to the fibrillar material adjacent to fascia adherens. No abnormalities in disc structure were found in any patient.

Contractile elements: The cytoplasm was filled with myofibrils, which often extended uninterrupted from one end of the cell to the other. Usually four to six sarcomeres were present in register across the cell (Fig. 4). Z bands, A bands, I bands and M lines were distinct. In two patients (Table II) focal thickening of the Z band and accumulations of abnormal Z band-like material were found in less than 1 percent of the cells examined (Fig. 5). In 90 percent of these cells the findings were confined to a single Z band and the abnormal Z band material extended irregularly into both adjacent sarcomeres. Rarely (in 10 percent of the cells affected), accumulated Z band material extended from Z band to Z band, partially obliterating entire sarcomeres but sparing adjacent sarcomeres.

Cell organelles: The nuclei were centrally placed and elliptical (Fig. 4), although occasional small invaginations of the cytoplasm into the nucleus were present. Nucleoli were frequent and occasionally multiple.

Mitochondria were interposed between sarcomeres although not with the regularity seen in ventricular muscle (Fig. 3 and 4). Aggregates of mitochondria were also present in the perinuclear areas (Fig. 4). The mitochondria were round to ovoid and varied considerably in size, ranging from 0.3 to 1.5 μ in diameter.

Glycogen, especially the beta particle type, was abundant and most prominent in the perinuclear region. The perinuclear region usually contained abundant atrial-specific granules and scattered lysosomal granules (Fig. 4). The atrial-specific granules measured from 0.15 to 0.4 μ in diameter and were invested by a membrane with a deeply staining homogeneous central core. These granules were also present beneath the sarcolemma and between sarcomeres.

A distinct Golgi apparatus with stacks of slightly dilated cisternae, 150 to 200 Å apart, and numerous vesicles ranging from 400 to 800 Å in diameter was present in the perinuclear region (Fig. 4). Irregular size tubules of the sarcoplasmic reticulum system were present throughout the cell. Their lumens ranged from 700 to 900 Å in diameter, and the tubules were often in close association to Z bands and the sarcolemma (Fig. 2). Ribosomes were occasionally found associated with the sarcoplasmic reticulum near subsarcolemmal cisternae and in the perinuclear region.

Scattered lipid droplets, usually in close association with mitochondria, were found. Intramitochondrial glycogen and occasional accumulations of lipochrome pigment were present.

Right Atrial Structure in Endocardial Cushion Defect

Two distinct populations of cells were found in the six patients with an endocardial cushion defect. All six patients had evidence of cell hypertrophy, defined as increased cell size, increased numbers of myofilaments, lobated nuclei and focal widening of Z bands. Two patients (Cases 9 and 11) had degenerating cells as well as hypertrophic cells (Table II). Degeneration was defined as myofibrillar loss with preferential loss of thick filaments, focal accumulation of sarcoplasmic

reticulum tubules, aggregation of mitochondria and glycogen granules replacing myofibrillar elements, and the presence of myelin figures and lysosomal bodies. Focal accumulations of Z band material, even with loss of thick filaments in adjacent sarcomeres, were not considered evidence of cell degeneration.

Hypertrophied Cells

Cell size and interstitium: The hypertrophied cells measured from 12 to 18 μ in diameter at the level of the nucleus. In two patients (Cases 9 and 11) the cells were as large as 24 μ in diameter. All six patients had increased amounts of interstitial and subendocardial connective tissue (Fig. 6). This was most pronounced in Cases 9 and 11, in which bundles of atrial muscle cells were separated from one another by prominent bundles of collagen. Fibroblasts were prominent. Elastic fibers were present in the subendocardium but did not appear to be increased in number. Blood vessels and nerves appeared normal in all six patients.

Sarcolemma and specialized junctions: The sarcolemma and the basement membrane investing the hypertrophied atrial cells were identical with those in patients with a ventricular septal defect. Focal subsarcolemmal accumulations of Z band material were also present. The hypertrophied cells were irregularly shaped and multiple cell processes were joined to several adjacent cells by both end to end and side to side intercalated discs (Fig. 7). In all but Patient 10, approximately



FIGURE 5. Case 4. Focal irregular accumulations of Z band-like material (**arrows**) in an otherwise normal right atrial cell from the heart of a patient with a ventricular septal defect. These large thickenings are isolated and do not affect adjacent sarcomeres. (×12,800, reduced by 23 percent.)

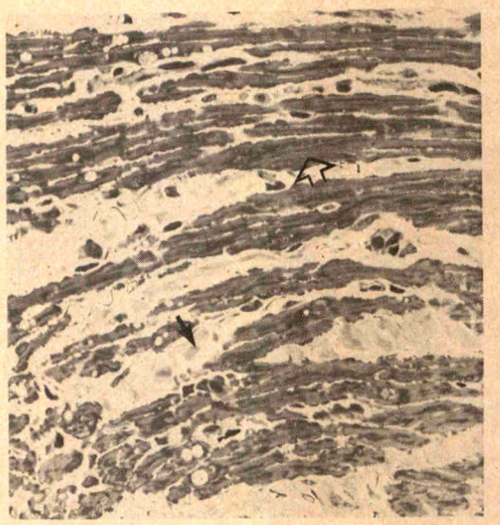


FIGURE 6. Case 7. Portion of the right atrial free wall from the hear of a patient with an endocardial cushion defect. By light microscop the atrial cells are large (**open arrow**), and the interstitial connectiv tissue (**solid arrow**) is prominent, often widely separating groups of cells (Toluidine blue ×208, reduced by 23 percent.)



FIGURE 7. Case 7. The hypertrophied cells from the heart of a patient with an endocardial cushion defect are irregular in contour with multiple intercalated discs (ID), of both the side to side and the end to end variety. The sarcomeres are still in register across the cell, but there are increased numbers of mitochondria (M) and more glycogen (**arrow**) between myofibrils. Accumulations of Z band-like material (Z) are also present. (×9,500, reduced by 23 percent.)

1 percent of the discs were markedly irregular in contour and were associated with increased deposition of Z band-like material and increased accumulations of fibrillar material especially at the fascia adherens (Fig. 8). The fibrillar material extended in irregular fashion into the cells and often appeared to merge with adjacent sarcomeres. The irregular discs measured up to 15 μ in length and 3 μ in width (discs measured up to 8 μ by 1 μ in nonhypertrophied cells).

T tubules were occasionally seen, especially in the larger atrial cells (Fig. 9). Increased numbers of T tubules have been reported in hypertrophied atrial cells[8]; however, T tubules were not found in the majority of hypertrophied cells in our study. Coated vesicles were more numerous than in atrial cells from patients with ventricular septal defects. Segments of rough sarcoplasmic reticulum were prominent especially beneath the sarcolemma in hypertrophied cells, and segments of the sarcoplasmic reticulum, extended junctional sarcoplasmic reticulum,[25] were prominent over Z bands.

Contractile elements: The sarcomeres were intact and well ordered although frequently 10 to 15 sarcomeres were present across the width of the hypertrophied cells (Fig. 7). In all six patients there were abnormal focal accumulations of Z band-like material (Table II). Accumulations of Z band-like material were most pronounced in Cases 9 and 11. The abnormal accumulation of Z band-like material included not only thickening of Z bands but extension of Z band-like material from Z band to Z band obliterating entire sarcomeres, and streaming of Z band-like material through the cytoplasm

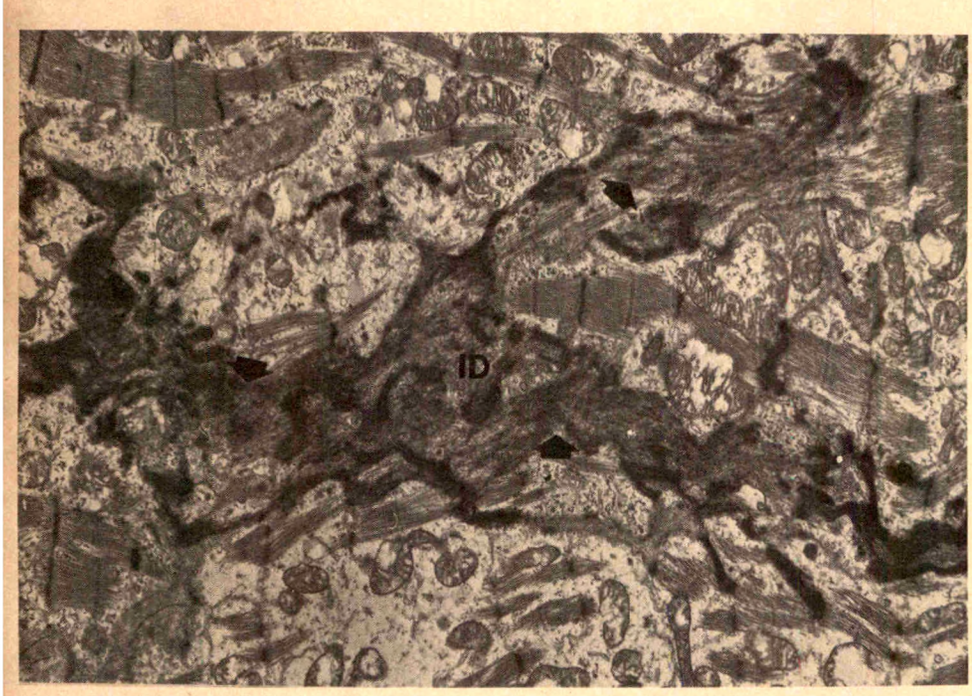


FIGURE 8. Case 12. The intercalated disc (ID) in this hypertrophied right atrial cell from the heart of a patient with an endocardial cushion defect is widened and irregular in contour. There is an increased amount of fibrillar material (**arrows**) associated with the fascia adherens junction, which extends into adjacent sarcomeres. (×12,400, reduced by 23 percent.)

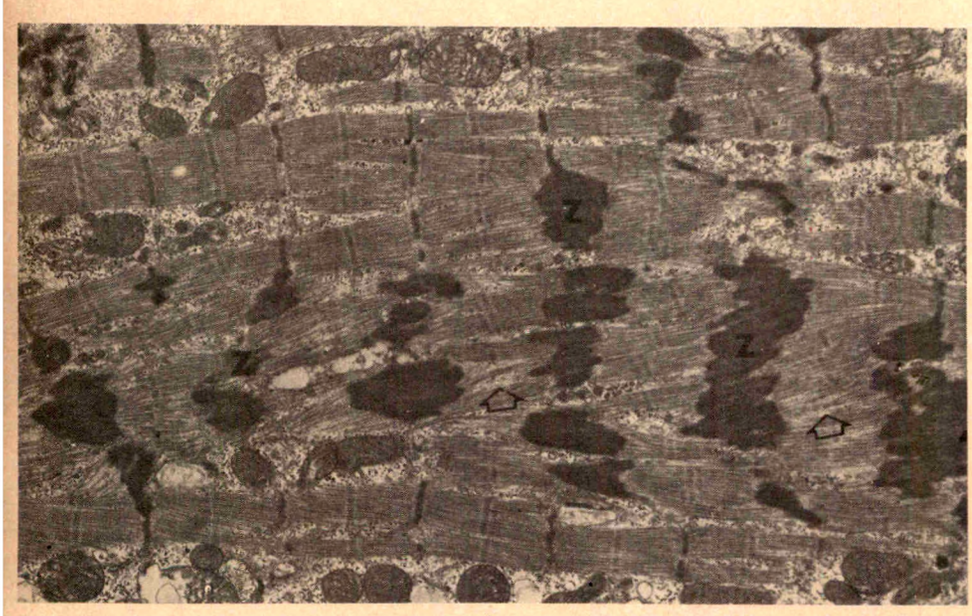


FIGURE 9. Case 12. Abnormal accumulations of Z band-like material (Z) in a hypertrophied right atrial cell from the heart of a patient with an endocardial cushion defect. The abnormal Z band material appears to extend along Z bands into adjacent sarcomeres. There is focal disorganization of myofilaments with apparent loss of thick filaments (**arrows**) adjacent to the abnormal accumulations of Z band-like material. (×15,700, reduced by 23 percent.)

to adjacent sarcomeres (Fig. 9). In sarcomeres adjacent to areas of extensive accumulation of Z band-like material there was focal disorganization and even loss of myofilaments.

Cell organelles: The nuclei were large with deep invaginations of the nuclear membrane dividing the nucleus into two or more distinct lobes. Multinucleated cells were not seen. The mitochondria were identical to those of the atrial cells from patients with a ventricular septal defect. Giant mitochondria were not found. Glycogen was abundant and atrial specific granules were present.

Degenerative Cells

Degenerative changes were found in Patients 9 and 11. In both these patients less than 5 percent of the cells examined demonstrated these changes (Table II) and the majority of the cells had the changes of cell hypertrophy described earlier.

Cell size: The cells with severe degenerative changes measured 8 to 10 μ in diameter (Fig. 10); the hypertrophied nondegenerating cells in the same patients were generally greater than 18 μ in diameter. Cells with moderate degenerative changes (Fig. 11) were intermediate in size, measuring 12 to 16 μ in diameter. Atrophic cells (diameter less than 5 μ) were not found.

Sarcolemma and specialized junctions: The sarcolemma was intact and had a normal appearance. Subsarcolemmal accumulations of Z band material (Fig. 12) were numerous in all degenerating cells and clusters of thin filaments were often attached to these deposits. The basement membrane of the degenerating cells was thickened, measuring up to 700 Å in thickness (Fig. 12). Occasional apparent widening of the undifferentiated portions of the intercalated discs were found between degenerating cells (Fig. 10, inset); however, loss of intercell connections was not a feature of the degenerating cells in our material, and the majority of discs were normal The widened irregular discs found in hypertrophied cells were not conspicuous in degenerating cells.

Contractile elements: Degenerating cells were charac terized by loss of sarcomeres and myofilaments and accu mulation of glycogen and mitochondria in areas of sarcome loss. In severely degenerating cells only scattered myofibrilla elements could be identified (Fig. 10). These cells containe masses of Z band material and aggregates of thin filament suggesting a disproportionate loss of thick filaments (Fig. 12 In cells with moderate degeneration the remaining sarcomere were disordered, often coursing at right angles to one anothe and there was focal loss of thick filaments in the remainin sarcomeres (Fig. 11). Accumulations of abnormal Z ban material were numerous in these cells.

Cell organelles: The cytoplasm of severely degeneratir cells was filled with glycogen and numerous small, irregula often elongated mitochondria with dense matrixes (Fig. 10 Many of the mitochondria were vacuolated, but mitochondri dense granules were not found. Tubules of the sarcoplasm reticulum were prominent and generally collapsed. There we numerous aggregates of mitochondria or accumulations sarcoplasmic reticulum tubules (Fig. 10). The cytoplas contained disarrayed clumps of short cytoskeletal fibri measuring 100 Å in thickness (Fig. 12). Intramitochondri glycogen of the beta particle type and lipid droplets (Fig. 1 were numerous. Large lysosomal granules and myelin figur were present in only scattered degenerating cells. Atrial sp cific granules were present, although they were less numero than in hypertrophied and normal atrial cells.

In cells with moderate degenerative changes large are of the cytoplasm were filled with aggregates of glycogen an mitochondria (Fig. 11). These areas of mitochondrial an glycogen accumulation were interspersed between inta bundles of myofibers. The mitochondria were generally un form in size with distinct cristae. No aggregates of sarcopla mic reticulum tubules were found. Atrial-specific granul were more numerous than in the severely degeneratir cells.

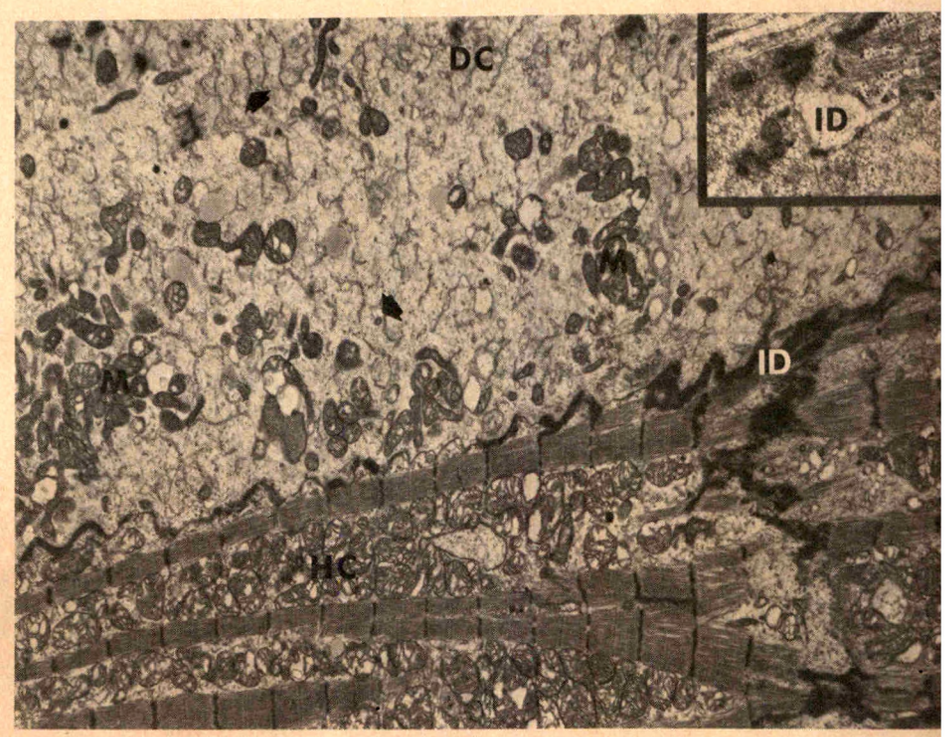


FIGURE 10. Case 9. Degenerating (DC) and hypertrophied (HC) cells from the right atrium of a patient with an endocardial cushion defect. The degenerating cell is characterized by extensive loss of myofilaments and aggregates of mitochondria (M), glycogen and segments of sarcoplasmic reticulum (**arrows**). Lipid droplets are abundant. The degenerating cell (DC) is joined to a hypertrophied cell (HC) by a well developed normal intercalated disc (ID). Dilated segments of the undifferentiated portions of intercalated disc are occasionally present between degenerating cells (**inset**). (×9,100, inset ×16,600, both reduced by 24 percent.)

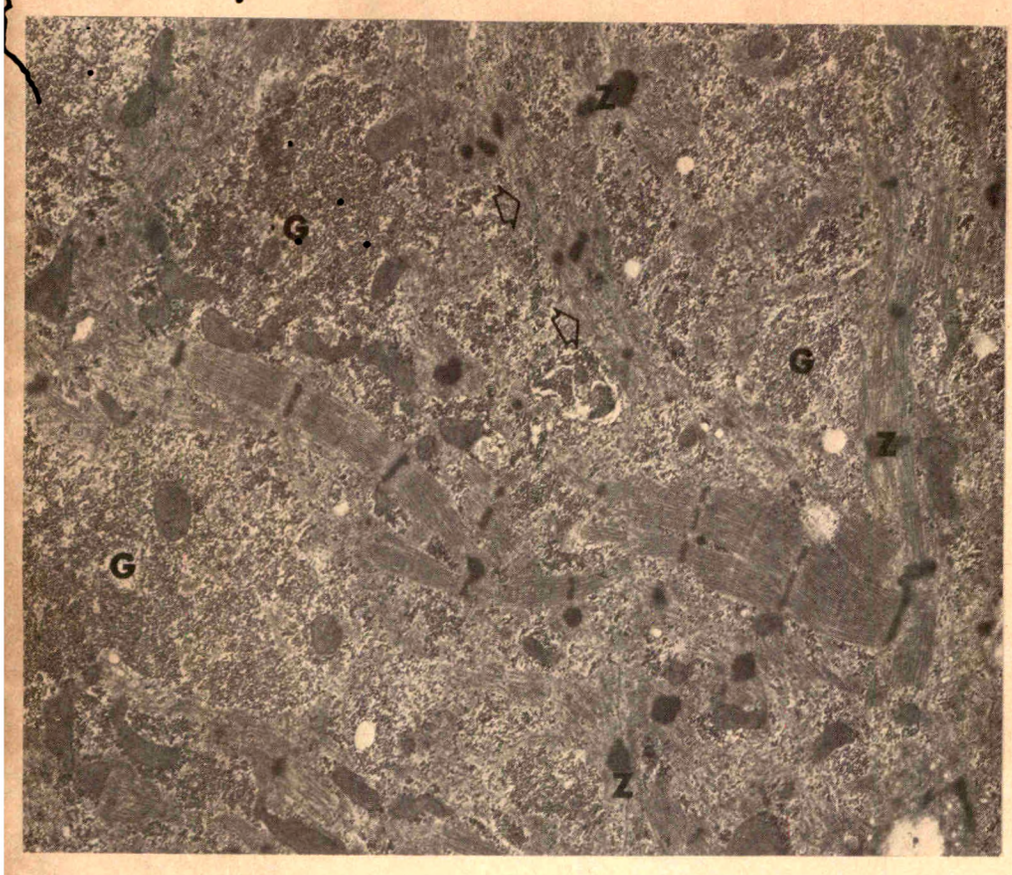


FIGURE 11. Case 11. Right atrial cell from the heart of a patient with an endocardial cushion defect with early or moderate degenerative changes. There is focal loss of contractile elements which are replaced by accumulations of glycogen (G). In the remaining sarcomeres there is apparent preferential loss of thick filaments (**arrows**). Many of the remaining sarcomeres appear to course at right angles to one another. Accumulations of abnormal Z band-like material (Z) are frequent. (×12,400, reduced by 21 percent.)

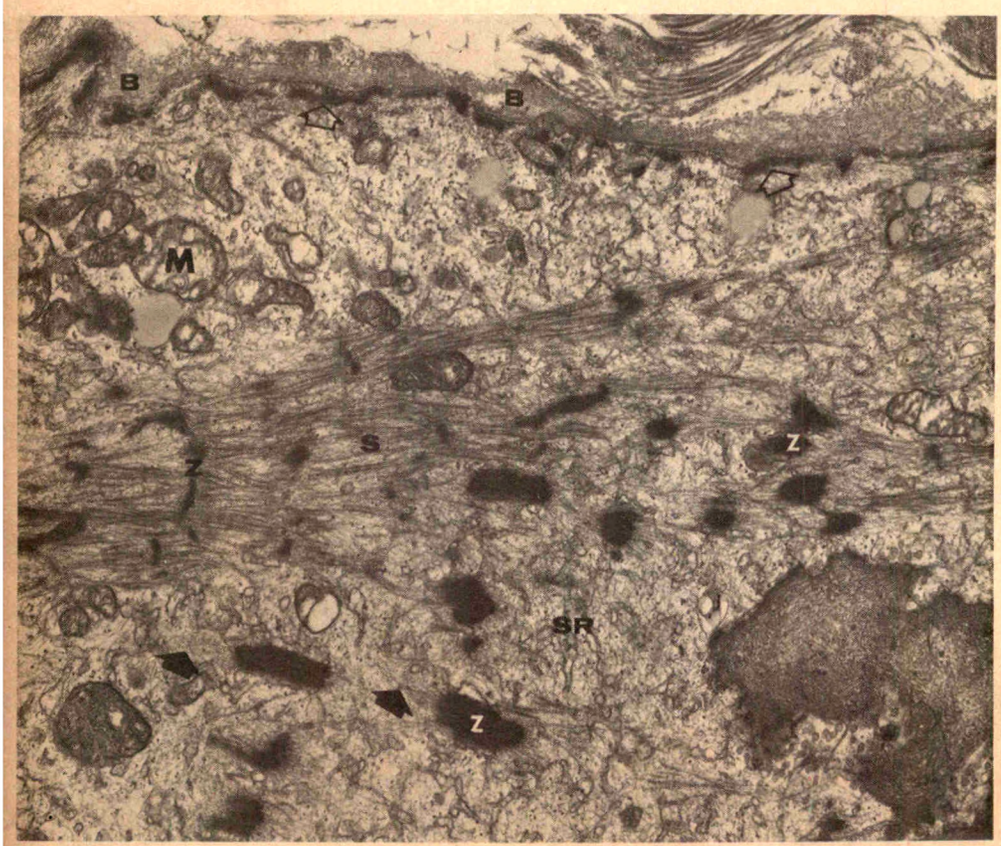


FIGURE 12. Case 11. The basement membrane (B) in this severely degenerating cell from the heart of a patient with an endocardial cushion defect is markedly thickened, measuring up to 700 Å. The cell contains remnants of sarcomeres (s) and tangles of short cytoskeletal fibrils (**solid arrows**). The mitochondria (M) are irregular in size and shape and focally vacuolated. Accumulations of Z band-like material (**open arrows**) are present beneath the sarcolemma, and dilated segments of sarcoplasmic reticulum (SR) are numerous. (×21,500, reduced by 21 percent.)

Discussion

The right atrium in ventricular septal defect (no evidence of cell hypertrophy): Our study has shown that there is a significant difference between the ultrastructure of right atrial cells in patients with a ventricular septal defect and in patients with an endocardial cushion defect. The right atrial myocardium in patients with a ventricular septal defect closely resembled the structure of normal mammalian atrial myocardium, especially that of the cat.[17] The only major difference between the ultrastructure of feline atria and human right atria from patients with a ventricular septal defect was cell size. In the cat the atrial muscle cells measured from 5 to 11 μ in diameter, averaging 5 to 6 μ, whereas in patients with a ventricular septal defect the atrial muscle cells measured 6 to 12 μ in diameter, averaging approximately 8 μ. This difference in cell size may reflect a species difference. It also may be secondary either to differences in the methods of fixation or to underlying disease. The cat atria were stretched and then fixed so that the sarcomeres were uniformly 2.2 μ in length.[17] Our human material was not stretched before fixation and, although many of the sarcomeres measured 2.2 μ in length, more often sarcomere length was closer to 2.0 μ because cells contract in the fixative. This difference in sarcomere length could partially explain the difference in average cell size because contraction may increase cell diameter.[26] The difference in cell size may also be secondary to the underlying disease. Scattered Z band changes were found in the atria of two patients with a ventricular septal defect. Such Z band changes have been described in hypertrophied human ventricular and atrial myocardial cells.[4,8]

There is no reason to expect the right atrium of the six patients with a ventricular septal defect in this study to be hypertrophied or otherwise abnormal. The left to right shunt was across the ventricular septum, and therefore there was no increase of blood flow through the right atrium.[27] The right atrial pressures were normal in all six patients, as was the size of the right atrium at operation. Structurally the changes associated with myocardial cell hypertrophy (lobation of nuclei, irregular cell shape, increased rough sarcoplasmic reticulum and increased interstitial connective tissue) were not present in any of these six patients. Although we cannot exclude the possibility that the right atrial myocardium of these patients is mildly hypertrophied, the lack of structural findings of hypertrophy is against this interpretation. Furthermore, the right atrial myocardium of these patients is nearly identical, structurally, to the atrial myocardium of normal cats.[17] Because normal atria from normal human subjects are not available for ultrastructural comparison, we have assumed that the ultrastructure of the right atrium from patients with a ventricular septal defect is representative of normal human atrial structure and have tentatively assigned 12 μ as the upper limit of normal for human right atrial cell size.

The right atrium in endocardial cushion defect (evidence of cell hypertrophy and degeneration): In contrast to patients with ventricular septal defect, changes of both cell hypertrophy and cell degeneration were found in the patients with an endocardial cushion defect. These structural changes were qualitatively similar to those described in the left atrium of patients with mitral valve disease.[8,25] The hypertrophied cells varied in size but were always greater than 12 μ in diameter and were often up to 18 to 24 μ in diameter. Other changes indicative of hypertrophy included irregular cell shape, highly lobulated nuclei, multiple intercalated discs, increased numbers of ribosomes and coated vesicles, prominence of the sarcoplasmic reticulum adjacent to Z bands and abnormalities of Z band material. Multinucleated cells and giant mitochondria reported in hypertrophied left atrial cells from patients with mitral valve disease[8] were not found. Changes of the intercalated disc in hypertrophied right atrial cells were also observed. These changes, including irregular widening of the disc and increased fibrillar material associated with fascia adherens junctions, have not been previously described in hypertrophy. In addition, there was increased interstitial connective tissue in each of the patients with an endocardial cushion defect. Increases in interstitial connective tissue are known to accompany cell hypertrophy at least in the ventricle.[1]

The degenerative changes in patients with an endocardial cushion defect, although similar to those described in the left atrium of patients with mitral valve disease,[8] were neither as extensive nor as severe. Loss of cell to cell junctions prominent in patients with mitral valve disease, was not seen, although the undifferentiated portion of the intercalated disc was occasionally dilated in the severely degenerating cells. Similarly, atrophic degenerating cells, less than 6 μ in diameter, were not present.

Degenerative changes in the ventricular myocardium have been extensively described,[4–7] especially in patients with congenital heart disease,[4] aortic valve disease[7] or cardiomyopathy.[5] These degenerative changes have been interpreted as manifestations of the end stage of cell hypertrophy,[6] because they are often found in association with marked cell hypertrophy. It is also possible that different factors are responsible for cell hypertrophy and cell degeneration.

The changes in right atrial structure in patients with an endocardial cushion defect appear to be related to the alterations in atrial hemodynamics. Hypertrophic changes were present in all six patients with increased right atrial blood flow and were most pronounced in the patients with the highest mean right atrial pressure. Degenerative changes were found only in the two patients with the highest right atrial pressure. This suggests that either increased blood volume or increased pressure or both, may result in right atrial hypertrophy, whereas increased pressure may be directly related to degenerative changes in the right atrium.

Functionally the loss of sarcomeres in degenerating cells suggests that these cells are not capable of con-

tracting. If enough cells in the atrium were similarly damaged the atrium would be unable to contract effectively during systole. The thickening of the basement membrane and dilatation of the undifferentiated portions of the intercalated disc might also alter the electrical properties of these degenerating cells, and these cells may be important in the genesis of atrial arrhythmias. In contrast to degenerating cells, the hypertrophied cells may function normally although increased in size.

Implications: The changes in cell ultrastructure that occur as a result of increased atrial volume and pressure in patients with an endocardial cushion defect may not be reversed when the defect is surgically corrected. Although there is evidence that cell hypertrophy in ventricular muscle subsides when the inducing stimuli are removed,[1] degenerative changes probably cannot be reversed. If such changes are a cause of abnormal atrial function, functional abnormalities may persist after surgery.

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Electrophysiologic Studies in Tricuspid Atresia

MARIA SERRATTO, MD, FACC
DEVKISHIN B. PAHLAJANI, MD, FACC*

Chicago, Illinois

Five patients with tricuspid atresia underwent His bundle studies with the recording catheter placed close to the mitral valve ring. Right atrial pacing and measurement of the refractory periods were performed in three. The prolonged intraatrial conduction time found in all patients is thought to be caused by a hypertrophied and dilated right atrium with increased internodal distance due to stretching of internodal pathways. The A-H interval was normal in all; the H-V interval was short in three and normal in two. The pattern of left axis deviation in the group with a short H-V interval is thought to be due to early origin of the posterior branches of the left bundle branch from the bundle of His and early activation of the posteroinferior parts of the left ventricle. The pattern of left axis deviation in the group with a normal H-V interval may be related to the previously reported anomalous course of the left bundle. Atrial pacing produced a normal response. The refractory periods were within normal range suggesting functional integrity of conduction through the atrioventricular node and bundle branches.

Tricuspid atresia is characterized by absence of the tricuspid valve orifice, a hypoplastic right ventricle, hypertrophy of the atria, interatrial communication and left ventricular hypertrophy. The great arteries may be normally related or transposed. The characteristic electrocardiographic findings include the patterns of biatrial enlargement, left axis deviation and left ventricular hypertrophy. The pattern of left axis deviation has been attributed to congenital fibrosis of left bundle branches and abnormalities in the peripheral portions of the conduction system of the left ventricle.[2] Recent histologic studies[3,4] of the conduction system in tricuspid atresia have challenged the validity of these assumptions. We therefore performed electrophysiologic studies (1) to investigate whether these morphologic features of the conduction system in tricuspid atresia could be correlated with the functional status of the conduction system, and (2) to explain the mechanism of abnormal conduction pattern in this congenital anomaly.

Material and Methods

Five children, aged 6 to 14 years (mean 11 years), with tricuspid atresia and normally related great arteries underwent His bundle studies performed with the technique described by Scherlag et al.[5] Informed consent of the child's parents was obtained in all cases. All patients had a 15 lead scalar electrocardiogram, a vectorcardiogram and hemodynamic evaluation at the time of electrophysiologic study.

The method was modified by placing a tripolar catheter close to the mitral valve near the atrioventricular (A-V) ring. The His bundle potential can be easily recorded from the left side of the septum.[6] The electrode catheter was positioned in the proper septal location, being advanced from the right femoral vein across the atrial septal defect and the mitral valve, forming a loop in the left ventricle. In three patients (Cases 3 to 5) the tripolar catheter was passed retrograde b

From the Division of Pediatric Cardiology, Cook County Children's Hospital, and the Hektoen Institute for Medical Research, Chicago, Illinois. This study was supported by the Children's Heart Research Foundation, Evanston, Illinois. Manuscript received June 6, 1978; revised manuscript received July 18, 1978, accepted July 19, 1978.

* Present address: L.T.M. Medical College, Sion, Bombay, India.

Address for reprints: Maria Serratto, MD, Cardiovascular Laboratory, Cook County Children's Hospital, 700 South Wood Street, Chicago, Illinois 60612.

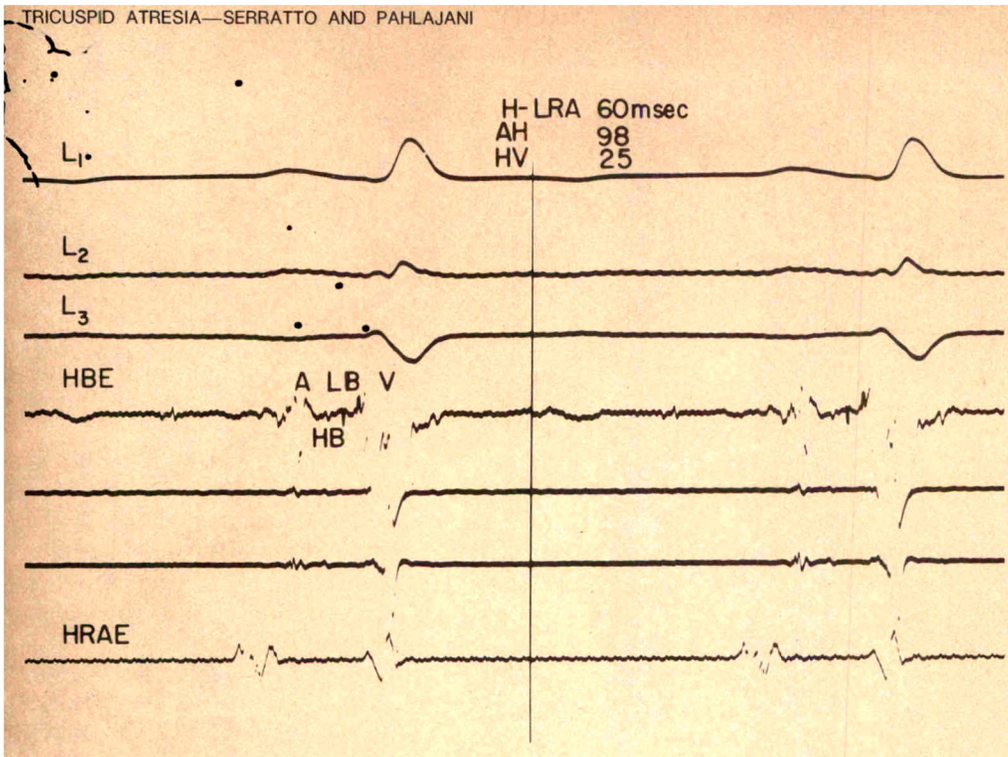


FIGURE 1. Patient 3. Standard electrocardiographic leads I, II and III (L_1, L_2, L_3), His bundle electrogram (HBE) and high right atrial electrogram (HRAE). Time lines = 1 second; paper speed = 200 mm/sec. Tracings show a normal P-R interval (0.155 second), prolonged intraatrial conduction time (H-LRA) (60 msec), a normal A-H interval (98 msec) and a short H-V interval (25 msec). The presence of both His bundle (HB) and left bundle (LB) depolarization excludes the possibility that the left bundle spike could be erroneously identified as the His bundle deflection. A = low right atrial deflection in the His bundle electrogram.

way of the right femoral artery and the aorta across the aortic valve using the method described by Rosen et al.[6] The electrodes were positioned against the ventricular septum near the A-V ring. Because His bundle and left bundle branch potentials can be recorded simultaneously from the left side of the septum,[6] an attempt was made to obtain both potentials in the same recording (Fig. 1). In Patient 5 the His bundle potential was recorded from both the right and left sides of the septum, the right ventricle being entered by way of the ventricular septal defect. His bundle pacing was not utilized for validation of His bundle potentials. Simultaneous electrocardiographic leads I, II and III were recorded. In three patients a quadripolar catheter was placed in the right atrium with its distal two poles positioned at the superior vena cava-right atrial junction for recording the high right atrial electrogram; the proximal poles were utilized for atrial pacing. The low right atrial electrogram was obtained from the tripolar catheter recording.

All recordings were made on an Electronics for Medicine DR 16 or a Hewlett Packard multichannel recorder at paper speeds of 100 and 200 mm/sec. A Grass stimulator, model DS88, was used for atrial pacing and delivering extrastimuli to the right atrium. The basic intervals and refractory periods were measured as described previously.[7]

Results

Electrophysiologic measurements (Table I): Intraatrial conduction time was measured as the duration of the P-A interval or of the high to low right atrial activation sequence, whichever was longer. This period was found to be prolonged in all five patients. Comparison with normal values obtained in our laboratory showed the difference to be statistically significant (normal subjects 25.78 ± 11.26 msec, patients with tricuspid atresia 55.00 ± 12.25 msec, $P < 0.01$). However, the refractory periods of the atrium, measured in three patients, were normal. The A-H interval was normal in all. The H-V interval was short in three patients (Fig. 1) and within normal limits in two. The refractory periods of the A-V node could not be determined because they were shorter than or equal to those of the atrium. Thus, conduction was atrium-limited, which is the most

TABLE I

Summary of Data in Five Cases

Case no.	P-R (sec)	Intervals: P-A and H-LRA (msec)	Intervals: A-H (msec)	Intervals: H-V (msec)	Response to Atrial Pacing	Refractory Periods (msec): Atrium	Refractory Periods (msec): A-V Node	Refractory Periods (msec): H-PS	RA Press (mm Hg)	Art O_2 Sat (%)
						ERP-FRP	ERP-FRP	ERP-FRP		
1	0.175	45/60	90	40	1:1 conduction at 180/min	290/300	. . .	. . .	*a* = 26; *v* = · · · m = 18	84
2	0.135	40	70	25	· · ·	. . .	. . .	. . .	*a* = 20; *v* = 10; m = 8	78
3	0.155	32/60	98	25	Wenckebach at 210/min	190/200	. . .	. . .	*a* = 11; *v* = 10; m = 7.2	84
4	0.167	17/45	100	50	Wenckebach at 210/min	180/190	. . .	. . .	*a* = 21; *v* = 10; m = 11	91
5	0.147	75	50	22	· · ·	. . .	. . .	. . .	*a* = 16; *v* = 10; m = 9	87

a = *a* wave; Art O_2 Sat = arterial oxygen saturation; A-V = atrioventricular; ERP-FRP = effective-functional refractory period; H-LRA = right intraatrial conduction time (high to low right atrium); H-PS = His-Purkinje system; m = mean; RA Press = right atrial pressures; *v* = *v* wave.

common pattern of A-V conduction in children.[7] Pacing in three patients produced a normal response.[7]

The electrocardiogram of all patients showed the patterns of biatrial enlargement, left axis deviation and left ventricular hypertrophy. The vectorcardiogram showed counterclockwise, superior QRS forces in the frontal plane.

Right atrial a *waves and mean pressures* were elevated in all patients (*a* wave 15 mm Hg, range 11 to 26; mean pressure 11 mm Hg, range 7 to 18). Arterial saturation ranged from 78 to 91 percent (mean 85).

Discussion

Intraatrial conduction time: Our studies suggest that patients with tricuspid atresia have prolonged intraatrial conduction time. This could result from an increase in internodal distance due to displacement of the A-V node or enlargement of the atria, or both, or from slowing of intraatrial conduction due to disease of the conduction pathways. Bharati and Lev[4] in their study of the histopathology of the conduction system in six cases of tricuspid atresia found that the central fibrous body was abnormally formed but that the A-V node and its approaches were in the normal position. Thus, the prolonged intraatrial conduction time is probably not due to displacement of the A-V node. The refractory periods of the atrium in our three cases were normal. Therefore, it is very unlikely that the prolonged intraatrial conduction time is due to disease of internodal pathways or scarring in the right atrium.[8] Because an interatrial communication is always present in tricuspid atresia and the hemodynamic burden on the right atrium will result in an enlarged and hypertrophied right atrium, it is conceivable that the internodal conduction distance will increase and the presence of the atrial septal defect may interfere with conduction through regular atrial muscle.[8,9] Our study of intraatrial conduction time allows another observation to be made. The P-R interval was normal in all patients. Thus, from the routine surface electrocardiogram, one could underestimate the degree of intraatrial conduction delay.

The A-H interval in all five patients was normal, and the response to atrial pacing was normal in three patients.[7] Refractory periods of the A-V node and His-Purkinje system could not be recorded in these three patients because the atrium was the limiting factor. However, these values were well within normal limits.[7]

Bundle of His and bundle branch conduction—the genesis of left axis deviation: The H-V interval was short in three patients and normal in two patients. Guller et al.[3] showed that the branches of the left bundl originated close to the junctional region, and the cours of the bundle was posterior to the defect. In some case studied by Bharati and Lev[4] the posterior fibers of th left bundle branch gave off early and continuously, an the bundle was shorter than normal. Such an anomalou course of the bundle and early origin of the posterio fascicle can give rise to early activation of the pos teroinferior part of the left ventricle, producing a pat tern of left axis deviation in the scalar electrocardiogran and counterclockwise superior QRS forces in the fronta plane of the vectorcardiogram. An early origin of th fibers of the left bundle will also result in a short H-V interval. These findings support the view that the ab normal left axis deviation and counterclockwise QRS forces in tricuspid atresia are not the result of fibrosi or disease of the left anterior fascicle but rather due t the early activation of the posteroinferior part of the lef ventricle, which in turn is related to the abnormal cours of the left bundle and early origin. Such an asynchro nous activation of the left ventricle has been found t be a mechanism of a similar electrocardiographic pat tern in endocardial cushion defects.[10,11]

Schatz et al.[12] described a case of tricuspid atresia i which the preoperative electrocardiographic pattern c left axis deviation changed to a pattern of right axi deviation in the postoperative period. This alteratio would exclude the possibility that the left axis deviatio in this lesion is due to block in the left anterior fascicle Moreover, in none of the cases studied by Bharati an Lev[4] and Guller et al.[3] was there any evidence of prox imal disease in the bundle branches.

In two of our cases the finding of a normal H-V in terval rules out the possibility of early activation of th posteroinferior part of the left ventricle. In these case the pattern of left axis deviation may be due to th anomalous course of the common bundle and the bundl branches, which are situated in the posterior wall of th ventricular septal defect, rather than to the early origi of the posterior fascicle.[3,4]

Pacing did not produce prolongation of the H-V in tervals, and the refractory periods of the A-V node an His-Purkinje system could not be reached because th atrium was the limiting factor in all. This normal re sponse suggests that the functional status of the dista conducting system is normal in tricuspid atresia, a hypothesis that correlates well with results of histo pathologic studies.[3,4]

Acknowledgment

Many thanks are due to Drs. K. M. Rosen and I. Carr fo reviewing the manuscript.

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Systemic and Pulmonary Hemodynamic Effects of Saralasin Infusion in Hypertension

Predictability of Plasma Renin Status From Hemodynamic Changes

SAKTI MOOKHERJEE, MD, FACC
ANIS OBEID, MD, FACC
ROBERT WARNER, MD
GUNNAR ANDERSON, MD
ROBERT EICH, MD
HAROLD SMULYAN, MD, FACC

Syracuse, New York

Hemodynamic measurements were obtained before and after 30 minutes of saralasin infusion in 26 fasting adults with hypertension (25 men and 1 woman). Nine showed a depressor response with a decrease in mean intraarterial pressure greater than 20 mm Hg. Ten were nonresponders and seven had an agonistic response with an increase in mean arterial pressure of greater than 10 mm Hg. Heart rate, pulmonary arterial and wedge pressures and pulmonary vascular resistance were nearly identical in the three groups and remained unchanged. Cardiac index decreased from a mean of 2.76 ± 0.14 (standard error of the mean) to 2.48 ± 0.1 liters/min per m^2 in the nonresponders ($P < 0.02$) but remained unchanged in the groups with a depressor or an agonistic response. The mean systemic vascular resistance decreased from 2,406 ± 303 to 1,839 ± 265 dynes sec/cm^5 in the group with a depressor response ($P < 0.001$) and increased in nonresponders (<0.02) and those with an agonistic response ($P < 0.01$). However, regardless of the response of mean arterial pressure, systemic vascular resistance decreased only in the 10 patients with a plasma renin activity greater than 5 ng/ml per hour (8 from the depressor response group and 1 each from the nonresponse and agonistic response groups).

It is concluded that (1) classification based solely on the response of arterial pressure to saralasin ignores important hemodynamic changes; (2) the response of cardiac index—no change in the patients with a depressor response and a reduction in nonresponders—suggests that endogenous angiotension II supports cardiac output in these groups; (3) a decrease in systemic vascular resistance is better than a decrease in mean arterial pressure as a predictor of the status of the plasma renin activity; and (4) lack of change in pulmonary vascular resistance suggests that endogenous angiotension II plays an insignificant role in maintaining the resistance of the pulmonary vasculature.

Intravenous infusion of saralasin acetate is being used as a screening test to detect the role of the renin-angiotensin system in the pathogenesis of hypertension.[1–5] Saralasin (1-sar-8-ala-angiotensin II) is a highly specific competitive analog of angiotensin II[6] and decreases arterial pressure in subjects with angiotensinogenic hypertension.[1–3] When hypertension is not dependent on increased angiotensin activity, the infusion of the angiotensin II analog may cause a pressor response, that is, a further increase in arterial pressure.[7–9] We undertook this study on the hemodynamic effects of saralasin infusion in hypertensive patients to clarify the role of endogenous angiotensin II in the systemic and pulmonary circulations in hypertension as well as the possible relation between the level of plasma renin activity and the response of the circulation to angiotensin II blockade.

From the Department of Medicine, Veterans Administration Hospital and State University Hospital, Syracuse, New York. This study was supported by Research Project 1368-02 of the Veterans Administration Hospital, Syracuse, New York. Manuscript received April 25, 1978; revised manuscript received July 5, 1978, accepted July 5, 1978.

Address for reprints: Sakti Mookherjee, MD, Cardiology Section, Veterans Administration Hospital, 800 Irving Avenue, Syracuse, New York 13210.

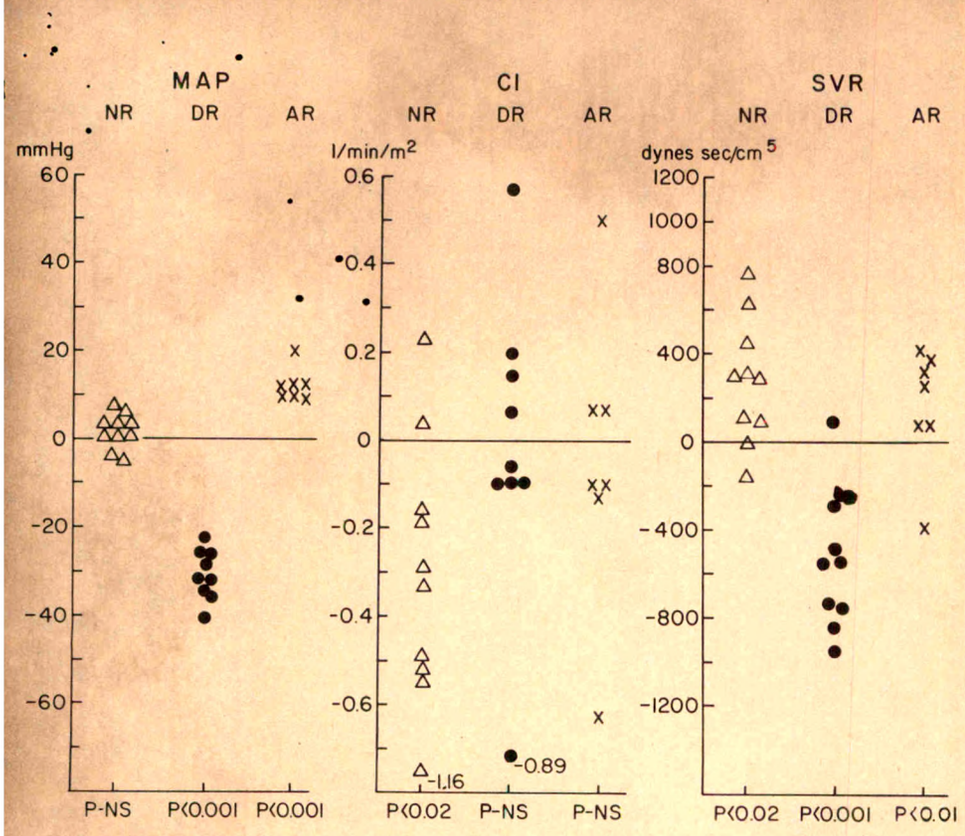


FIGURE 1. Changes in mean arterial pressure (MAP), cardiac index (CI) and systemic vascular resistance (SVR) with saralasin infusion. Cardiac index decreased in nonresponders (NR) with a slight increase in systemic vascular resistance. In depressor responders (DR) mean arterial pressure decreased because of a marked reduction in systemic vascular resistance. In the agonistic pressor responders (AR) the changes in cardiac index were variable, and systemic vascular resistance increased in six of seven patients. **Triangles** = nonresponders; **closed circles** = depressor responders; **crosses** = agonistic pressor responders. l = liter; NS = not significant; P = probability.

Patients and Methods

Patients: Twenty-six hypertensive patients, 25 men and 1 woman aged 26 to 67 years, were studied. Admitted for study of their hypertension, all underwent a history and physical examination, ophthalmoscopic study, chest X-ray examination, electrocardiogram, urinalysis and serum electrolyte determinations. The duration of hypertension ranged from a few months to several years, and two subjects had accelerated hypertension as indicated from the history, physical examination and ophthalmoscopic findings.[10] Five patients were receiving no antihypertensive medications. The remaining 21 had been taking a variety of antihypertensive drugs that were discontinued a week before the hemodynamic study. No patient was taking guanethidine or reserpine. Two patients with accelerated hypertension had received nitroprusside therapy until 30 minutes before the study. All other patients were ambulatory and on no special diet. All understood the investigational nature of the protocol and gave written consent before the procedure.

Hemodynamic measurements: With the patient in the postabsorptive state, right heart catheterization was performed through a right medial antecubital vein using a themodilution catheter placed in the pulmonary artery. Continuous monitoring of electrocardiographic lead II was instituted. The right brachial artery was cannulated percutaneously, and both brachial and pulmonary arterial pressures were displayed on the oscilloscope. After an equilibration period of at least 15 minutes marked by stability of vital signs, the control measurements were obtained of hemodynamic variables including heart rate, mean systemic arterial pressure and pulmonary arterial pressures (mean and diastolic). The mean pressures were obtained with electronic damping. Cardiac output was measured in triplicate using the thermodilution method and the average of the three serial determinations (variation less than 12 percent) was used to calculate cardiac index. The pulmonary and the systemic vascular resistances were calculated using standard formulas. Stroke volume index was measured as cardiac index divided by heart rate, and the stroke work index was calculated from the following formula[11]: SWI = SVI (MSP − PADP) × 0.0136 g-m/m^2 and MSP = 0.8 (arterial systolic pressure − arterial diastolic pressure) + arterial diastolic pressure[11]; where SWI = stroke work index, SVI = stroke volume index, MSP = mean systolic pressure and PADP = pulmonary arterial diastolic pressure.

The pulmonary arterial diastolic pressure in 16 patients with a satisfactory pulmonary capillary wedge pressure tracing was within ±3 mm Hg of the mean wedge pressure. Hence in this study the pulmonary arterial diastolic pressure will be used to represent the left ventricular filling pressure in all patients.[12] A 10 ml sample of blood was drawn from the pulmonary artery to determine control plasma renin activity using a radioimmunoassay technique.[13]

Saralasin infusion: After control hemodynamic measurements were obtained, an infusion of saralasin acetate in 50 ml of 5 percent dextrose in water was started at a test dose of 0.05 μg/kg per min using a Harvard infusion pump. Electrocardiographic leads and pulmonary and brachial arterial pressures were continuously monitored. If no untoward symptoms or signs were observed during 10 minutes of the test infusion, the dose of saralasin acetate was increased to 5 μg/kg per min and continued for 30 minutes. The hemodynamic measurements were repeated during the last 10 minutes of the infusion. For statistical analysis of the results, Student's *t* test for paired values was used and mean values were expressed with ± standard error of the mean.

Results

No untoward side effects occurred during or after infusion of saralasin. There was a transient initial increase of blood pressure in all patients at 2 to 5 minutes of the influsion (5 μg/kg per min). This hypertensive effect persisted only in those classified as agonistic pressor responders.

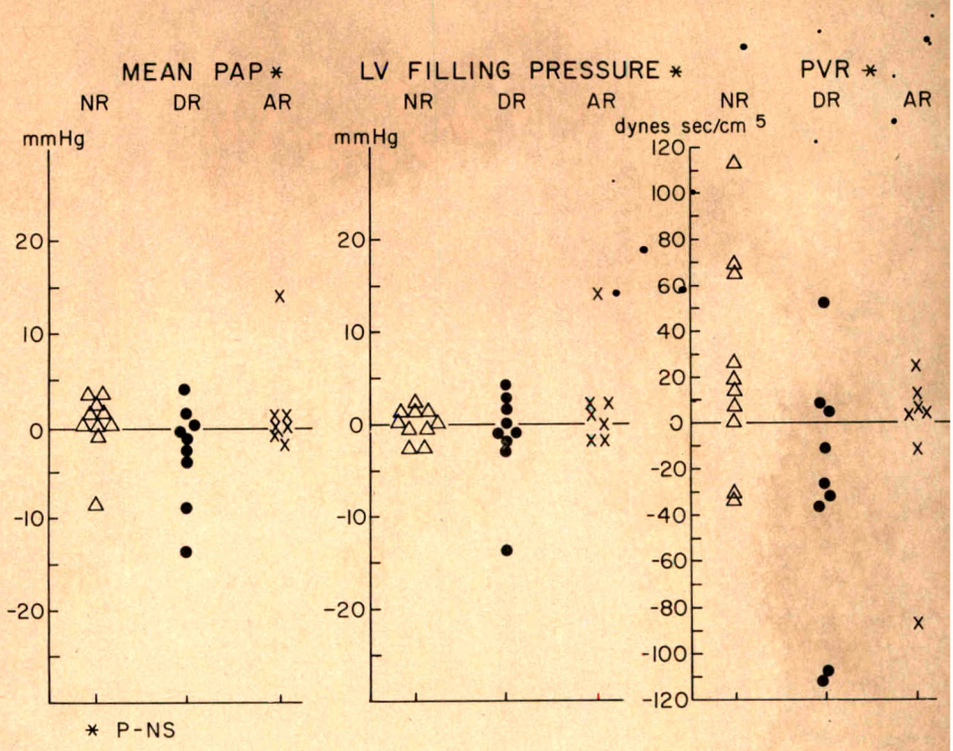


FIGURE 2. Changes in mean pulmonary arterial pressure (PAP), left ventricular (LV) filling pressure and pulmonary vascular resistance (PVR) with saralasin infusion. Symbols and abbreviations as in Figure 1. No significant change occurred in mean pulmonary arterial pressure, left ventricular filling pressure or pulmonary vascular resistance in any group with saralasin infusion.

Mean arterial pressure (Fig. 1): Depending on a sustained response of the mean intraarterial pressure to saralasin infusion at 20 minutes, the patients were classified into three groups: nonresponders, depressor responders and agonistic pressor responders.

Nonresponders: These 10 patients had a control average mean arterial pressure of 120 ± 9.5 mm Hg that remained essentially unchanged after saralasin infusion.

Depressor responders: In these nine patients the mean arterial pressure decreased by more than 20 mm Hg after saralasin infusion. The average control mean arterial pressure of 127 ± 6 mm Hg decreased to 94 ± 6 mm Hg in this group ($P < 0.001$).

Agonistic pressor responders: In these seven patients, the mean arterial pressure increased by more than 10 mm Hg after saralasin infusion. The mean arterial pressure increased from an average of 127 ± 8 to 139 ± 8 mm Hg ($P < 0.001$).

Cardiac index (Fig. 1): *In the nonresponders* this index ranged from 2.26 to 3.65 liters/min per m^2 (mean 2.76 ± 0.14) in the control state and decreased to a mean of 2.48 ± 0.1 liters/min per m^2 after saralasin infusion ($P < 0.02$).

In the depressor responders cardiac index ranged from 1.6 to 3.83 liters/min per m^2 (mean 2.5 ± 0.24) in the control state. Saralasin infusion resulted in an insignificant change (mean 2.47 ± 0.22 liters/min per m^2).

In the agonistic pressor responders cardiac index ranged from 2 to 3.49 liters/min per m^2 in the control state (mean 2.61 ± 0.2) and changed to a mean of 2.65 ± 0.17 liters/min per m^2 with the infusion of the drug (difference not significant). There was no significant difference in the control levels of mean cardiac index among the groups.

Systemic vascular resistance (Fig. 1): Calculated systemic vascular resistance increased in the nonresponders from a mean of 1,841 ± 173 to 2,096 ± 189 dynes sec/cm^5 ($P < 0.02$). It decreased in the depressor responders from a mean of 2,406 ± 303 to 1,839 ± 265 dynes sec/cm^5 ($P < 0.001$). In the agonistic pressor responders it increased in six of seven patients. It increased in this group from a mean of 2,008 ± 147 to 2,166 ± 183 dynes sec/cm^5 ($P < 0.01$).

Heart rate: Heart rate changed in nonresponders from a mean of 86 ± 3 to 88 ± 3 beats/min, in depressor responders from 84 ± 3 to 82 ± 3 beats/min and in agonistic pressor responders from 74 ± 3 to 73 ± 3 beats/min (all nonsignificant). Reflex tachycardia in the depressor responders or bradycardia in the agonistic pressor responders did not occur after the infusion of saralasin.

Stroke volume index: In nonresponders this index decreased from a mean of 32.9 ± 2.3 to 27.9 ± 1.5 ml/m after saralasin infusion ($P < 0.01$) and did not change significantly in the other two groups.

Stroke work index: In nonresponders this index decreased from a mean of 60.6 ± 6.5 to 55.2 ± 5g-m/m with saralasin as a result of a decrease in stroke volume index ($P < 0.01$). By contrast, in depressor responders stroke work index decreased from a mean of 65.6 ± 7.3 to 47.5 ± 4.9 g-m/m^2 ($P < 0.001$) as a result of a decrease in arterial pressure, and in agonistic pressor responders it increased from a mean of 73.8 ± 8.2 to 83.9 ± 8.4 g-m/m^2 because of an increase in arterial pressure ($P < 0.05$).

Pulmonary arterial pressure (Fig. 2): Mean pulmonary arterial pressure in nonresponders did not change from an average of 13 ± 2 mm Hg after saralasin infusion. In depressor responders it decreased from 16 ±2 mm Hg in the control state to 13 ± 1 mm Hg after drug infusion (difference not significant). In agonistic pressor responders it increased from an average of 13

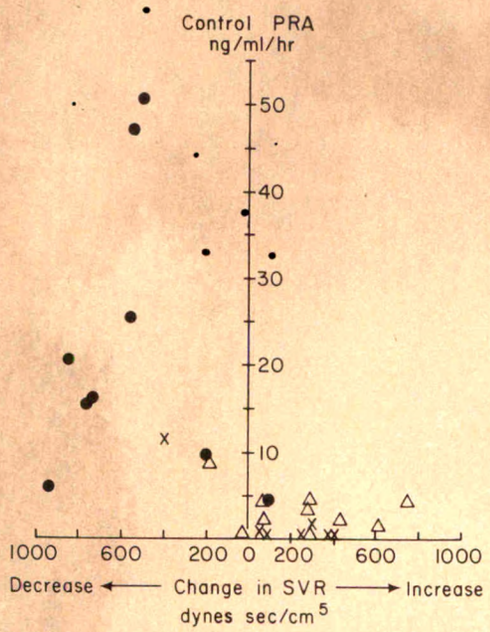


FIGURE 3. Relation between the level of control plasma renin activity (PRA) and change in systemic vascular resistance (SVR) with saralasin infusion. The levels of control plasma renin activity and changes in systemic vascular resistance in the same patients are presented on the vertical and horizontal axes, respectively. Symbols representing the three different groups as in Figure 1. Eight of nine depressor responders **(closed circles),** one nonresponder **(triangles)** and one agonistic pressor responder **(crosses)** had a plasma renin activity level above 5 ng/ml per hour, and systemic vascular resistance decreased significantly only in these patients.

± 1 to 15 ± 2 mm Hg (difference not significant). The pulmonary arterial diastolic pressure ranged from a mean of 8 to 9 mm Hg in all three groups in the control state and did not change significantly after saralasin infusion.

Pulmonary vascular resistance (Fig. 2): This measurement, which was in the normal range in all three groups in the control state, did not change significantly after the infusion. However, the changes tended to be in the same direction as those of systemic vascular resistance.

Plasma renin activity: Control mixed venous mean plasma renin activity was 3.35 ± 0.7 ng/ml per hour in nonresponders, 20.82 ± 8.2 in depressor responders and 2.14 ± 1.56 in agonistic pressor responders. Although plasma renin activity in depressor responders was much higher than in the other two groups (P <0.001), there was no significant difference between the levels of control plasma renin activity in the nonresponders and the agonistic pressor responders.

Relation between control plasma renin activity and the response of the mean arterial pressure and the systemic vascular resistance to saralasin infusion (Fig. 3): Eight of nine responders and one each from the nonresponder and agonistic pressor responder groups had control plasma renin activity of greater than 5 ng/ml per hour. The rest of the patients including one from the responder group had a plasma renin activity of less than 5 ng/ml per hour. However, regardless of the response of the mean arterial pressure to saralasin infusion, the systemic vascular resistance decreased only in patients whose control plasma renin activity was greater than 5 ng/ml per hour. Systemic vascular resistance decreased from a mean of 2,407 ± 267 to 1,829 ± 238 dynes sec/cm^5 (P <0.001) in these patients.

Discussion

These data show that saralasin infusion has complex hemodynamic effects on the cardiovascular system in hypertension. Some of these effects cannot be appreciated from the changes in arterial pressure alone. In nonresponders, for example, mean arterial pressure remained unchanged, whereas a significant decrease in cardiac, stroke volume and left ventricular stroke work indexes occurred with saralasin infusion. Nearly identical observations have also been made by previous investigators in animal experiments[14,15] and in human studies.[16,17]

Mechanisms of hemodynamic effects of saralasin: A decrease in cardiac index generally occurs as a result of one or more of the following mechanisms: (1) extreme change in heart rate—either markedly slow or very fast rates; (2) reduction in ventricular filling pressure resulting from a decrease in venous return or venodilatation; (3) increased resistance to the ventricular outflow, for example, from an increase in peripheral vascular resistance; and (4) decreased inotropic state of the myocardium.

Nonresponder group: In this group no significant change occurred in heart rate or left ventricular filling pressure. There was also no further increase in arterial pressure. Therefore the decrease in cardiac index in this group in the absence of venodilatation or increased outflow resistance may be related to a reduction in inotropic state of the heart resulting from the infusion of saralasin.

Depressor responder group: This group had a marked decrease in systemic valcular resistance that caused arterial pressure to decrease with no significant change in cardiac index. A reduction in arterial pressure due to a decrease in peripheral resistance in the absence of a concomitant change in heart rate or a decrease in left ventricular filling pressure, as might occur from venodilatation, would tend to increase the cardiac output unless a reduction in inotropic state of the heart occurred simultaneously.[18,19] Antihypertensive drugs causing little or no venodilatation but having predominantly an arteriolar dilating effect (for example, hydralazine) increase heart rate, cardiac output and pulmonary arterial pressure while decreasing systemic arterial pressure. In contrast, drugs producing both venodilatation and arteriolar dilatation (for example, sodium nitroprusside) do not stimulate the heart or increase pulmonary arterial pressure.[20] Saralasin acted as an arteriolar dilator, although indirectly, in the depressor responder group but did not cause any significant change in heart rate, cardiac output or pulmonary arterial pressure. Thus, in this group, one would also speculate among other factors a decrease in cardiac inotropy during saralasin infusion as a possible explanation for the lack of increase of cardiac index.

Borucki et al.[14] observed a decrease in arterial pressure with no change in cardiac output and no effect on venous tone after saralasin infusion in animals. Carvalho et al.[17] postulated either an alteration in venous return or an inhibition of myocardial contractility as the underlying mechanism of the effect of saralasin on cardiac performance in hypertensive patients. Our study, which included measurements of ventricular filling pressure, makes change in venous return or venodilatation rather unlikely to be an important factor influencing the cardiac performance during saralasin infusion. Therefore, inhibition of myocardial contractility, either local or mediated through the central nervous system, seems more likely.

Agonistic pressor responder group: Patients showing sustained agonistic pressor response, on the other hand, had a lack of significant change in cardiac output during saralasin infusion. This is contrary to the expected, in part reflex-induced, decrease in cardiac output when the arterial pressure increases due to an increase in systemic vascular resistance. It is conceivable that in this subgroup of patients the effect of saralasin mimicked that of angiotensin II, not only on the arteriolar level but also on the state of myocardial inotropy. The former effect would cause an increase in arterial pressure by increasing the systemic vascular resistance, and the latter would tend to raise the cardiac output. The net result of this interplay may explain the absence of a significant change in cardiac index in this group.

The mechanism of failure of the heart rate to vary significantly in response to saralasin-induced change in arterial pressure remains speculative. The possibility of drug-related interference with the baroreceptor mechanism cannot be excluded.

Role of endogenous angiotensin II: There is considerable controversy regarding the role of endogenous angiotensin II in circulatory support. In vitro experimental studies have shown a strongly positive inotropic effect of angiotensin II, probably mediated through the augmentation of calcium ion entry into the myocardium by an increase in transmembrane ion movements.[21–23] In one such study saralasin was noted to block this action of angiotensin II.[23] However, in intact animals as well as in human studies, infusion of angiotensin II has had variable effects on cardiac output. Although a positive inotropic effect—either direct, through the central nervous system or by way of release of catecholamines—has been suggested by some investigators,[24–26] others[27,28] have observed a negative inotropic effect. Obviously, the increase or decrease in cardiac output depends also on the effects of angiotensin II on the arteriolar resistance. If the predominant effect is a profound increase in peripheral resistance, cardiac output may decrease, whereas output may increase if the positive inotropic effect becomes predominant. In a given subject the net effect on cardiac output would depend on the interplay of these two factors.

Wallace et al.[16] found a reduction of cardiac output with angiotensin II blockade by saralasin infusion in many hypertensive patients and suggested a supportive role of endogenous angiotensin II in the maintenance of cardiac output. The mechanism of the effect of angiotensin II on the heart was thought to be either direct or mediated by way of the parasympathetic nervous system. Bravo and Tarazi[15] used atropine to reverse the bradycardia and cardiac output-lowering effect of saralasin in dogs. Our data showing a lack of significant response of the heart rate in all groups of hypertensive patients after saralasin infusion suggest that the changes in cardiac output are not likely to have resulted from parasympathetic overactivity.

In contrast to other hemodynamic studies with saralasin infusion,[14–17] our patients were not subjected to dietary salt restriction; nevertheless, the results are nearly concordant.

Role of Plasma Renin Activity

The relation between the response of systemic vascular resistance to saralasin infusion and control plasma renin activity is also intriguing. The systemic vascular resistance decreased in all patients whose control plasma renin activity level was above 5 ng/ml per hour. This decrease in systemic vascular resistance occurred irrespective of the response of arterial pressure to saralasin infusion. It was not the magnitude of the control systemic vascular resistance but its reduction that was predictive of the level of plasma renin activity of over 5 ng/ml per hour. The response of the mean arterial pressure alone would have failed to predict the level of plasma renin activity in three patients, one from each group. The decrease in systemic vascular resistance with saralasin infusion therefore appears to be a better indicator of the control level of plasma renin activity than the response of the mean arterial pressure in a given patient with hypertension. Although unrelated to saralasin, the contrast between the response of the systemic vascular resistance and mean arterial pressure in relation to the level of plasma renin activity has previously been observed in connection with the antihypertensive agent propranolol.[29]

The response of the pulmonary arterial or wedge pressure and pulmonary vascular resistance to saralasin infusion also merits comment. Lack of significant change in pulmonary vascular pressures or resistance in any subgroup of patients after saralasin infusion suggests that endogenous angiotensin II, although produced in the lung from angiotensin I, does not seem to play an important role in the pulmonary vasculature, that is, in the support of pulmonary vascular pressure or maintenance of pulmonary vascular resistance.

Implications: Thus, the angiotensin II analog saralasin not only is an important pharmacologic tool[30] in defining the role of the renin-angiotensin system in the pathogenesis of many hypertensive states but also permits studies to evaluate the part endogenous angiotensin II may play in the support of cardiac output in such cases. In addition, the results of infusion of the analog have suggested absence of an effect of endogenous angiotensin II on the pulmonary vasculature.

Acknowledgment

We thank Norma Hill, Janice Sroman and Glenn Mead of the cardiovascular laboratory. Eaton Laboratories of Norwich, New York supplied the saralasin.

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Long-Term Medical Management of Hypertrophic Obstructive Cardiomyopathy

MARTIN J. FRANK, MD, FACC
ABDULLA M. ABDULLA, MD
MARIO I. CANEDO, MD
ROBERT E. SAYLORS

Augusta, Georgia

Twenty-two patients, aged 15 to 61 years, with hypertrophic obstructive cardiomyopathy documented at catheterization were followed up prospectively for 2 to 8 years (mean 5) while receiving "complete" beta receptor blocking doses of propranolol (average dose 462 mg/day). Hypertension, fluid retention, pulmonary disease and arrhythmias were treated as required. Dyspnea, angina, syncope, presyncope and palpitations were graded from 0 to 3 based on severity, and the scores were added to obtain a total score. This group was compared with 14 nonrandomized control patients, aged 17 to 78 years, who were not receiving propranolol and were evaluated retrospectively for a mean follow-up period of 5 years (range 2 to 13). The average total score for the protocol group was initially 7.9 and is now 1.9. No patient died; the condition of all patients is improved, with an average improvement in dyspnea of 58 percent. Eighteen patients are currently asymptomatic during usual daily activities. In contrast, symptoms increased in severity in 13 of the 14 control patients. Their mean score increased from 2.9 to 5.4, and dyspnea increased by 133 percent. Of the 10 control patients treated only medically, 4 died suddenly.

Improvement in protocol patients was independent of the severity of subvalve obstruction. Potentially life-threatening arrhythmias were found in 11 of the 22 protocol patients, including the 3 patients without obstruction at rest. Rhythm disturbance responded to propranolol alone in four patients, but antiarrhythmic drugs or pacemaker insertion, or both, was required in the remaining seven patients. Thus, "complete" beta blockade supplemented by control of arrhythmia is optimal management for hypertrophic obstructive cardiomyopathy. Most patients do not require surgery.

Despite improvement in diagnosing and understanding the pathophysiology of hypertrophic obstructive cardiomyopathy, controversy exists concerning methods of management. Some investigators[1,2] believe that surgery is preferable for patients with important symptoms and obstruction at rest. Although a recent study[3] reported no deaths after 30 surgical procedures, an average surgical mortality rate of 14 percent has been reported for left ventriculomyotomy and myectomy.[3–7] Moreover, the surgical approach evidently does not eliminate late deaths. Wigle et al.[1] reported three operative deaths among 31 surgically treated patients (9.7 percent mortality rate), and 4 additional deaths 3 to 7 years later (overall mortality rate 22.5 percent). The average follow-up period for this group was 53 months. Although these patients had had severe outflow obstruction and physical disability, late fatalities were sudden, unexpected and unrelated to functional status. This outcome differs little from that in patients not treated surgically.[8–10] Because the annual mortality rate of patients with this condition is almost 4 percent,[2,8–10] four or five deaths would be predicted for such a group followed up

From the Division of Cardiology, Department of Medicine, Medical College of Georgia, Augusta, Georgia. The early part of the project was carried out during Dr. Frank's tenure as a Senior Investigator of the Georgia Heart Association, Augusta, Georgia. Manuscript received March 8, 1978; revised manuscript received June 20, 1978, accepted July 5, 1978.

Address for reprints: Martin J. Frank, MD, Medical College of Georgia, Division of Cardiology, Augusta, Georgia 30901.

medically for the same period (about 15 percent mortality rate). The mortality rate did not decrease in these patients, although 21 of the 24 survivors of surgery had symptomatic improvement.

Opinions about medical management also differ. Although most authors agree that beta adrenergic blockade benefits patients with latent obstruction, patients with significant obstruction at rest and important symptoms, particularly dyspnea, seem to do less well.[1,2] We have been interested in the nonsurgical management of hypertrophic obstructive cardiomyopathy since 1968, when the first patient entered this study. Our approach to therapy has changed considerably since then. This report was prepared because (1) few evaluations of long-term medical treatment have been published, (2) accounts of doses of propranolol greater than 240 mg daily are rare, (3) the adequacy of beta adrenergic blockade has not been emphasized,[11–15] and (4) the management of problems not necessarily related to the obstructive component has received scant attention. This report is based on our experience with 22 patients followed up for 110 patient years.

Methods

Patient Selection

Computer search permitted the identification of 70 patients with hypertrophic obstructive cardiomyopathy referred to this institution since 1958. The diagnosis was confirmed in all patients with cardiac catheterization, echocardiography or autopsy, or a combination of these. The patients were classified into four groups.

The first group included 22 patients who fulfilled the following criteria for selection: (1) symptomatic disability due to hypertrophic obstructive cardiomyopathy; (2) a willingness to undergo diagnostic cardiac catheterization and angiography to establish a hemodynamic baseline; (3) the presence of a resting or provocable gradient (premature ventricular beats or isoproterenol stimulation); (4) an initial willingness to return at necessary intervals for periodic evaluation; and (5) a follow-up period of at least 2 years. Because exacerbations and remissions are known to occur during the course of hypertrophic obstructive cardiomyopathy, a follow-up period of at least 2 years was considered necessary to gauge accurately the effectiveness of medical therapy. No patient was excluded because of severe disability, congestive heart failure or atrial fibrillation, although all patients were initially in sinus rhythm. *A second group of 18 patients are currently following our protocol* but have been excluded from the study because they have been followed up for less than 2 years. No patient has been lost to follow-up or has died.

The third group is an untreated control population of 14 patients followed up for more than 2 years. These patients were selected retrospectively, and only three were available for repeat evaluation. Thirteen patients did not receive propranolol, either because the drug was not available or because the primary physician believed that the drug was not required. The 14th patient never received more than 80 mg/day of propranolol.

The fourth group included the remaining 16 patients, most of them also identified retrospectively. Nine patients have been located and are known to be alive and taking propranolol in varying amounts, but they are unwilling or unable to follow our protocol and have not been reevaluated after starting therapy. Four patients lost to follow-up in less than 2 years were not taking propranolol. Mitral valve infectious endocarditis and congestive heart failure developed in one of the remaining three patients, and he died immediately after cardiac catheterization. Another patient died from congestive heart failure 10 years after a myotomy-myectomy at another institution, and the third patient died of unrelated causes.

Symptom Scores

Each of the 22 patients in the protocol group was questioned concerning the severity of symptoms known to be related to the disease: dyspnea, chest pain, syncope, presyncope (dizzy spells) and palpitations. The symptoms were graded, using modified New York Heart Association criteria, as follows:

Dyspnea: 0 = none, 1+ = dyspnea only at greater than ordinary activity, daily routine slightly compromised, 2+ = dyspnea occurring with ordinary activity, daily routine moderately compromised; and 3+ = dyspnea occurring with less than ordinary activity, daily routine severely compromised. This symptom was the most difficult to evaluate. When the grade was unclear, we used the Bruce exercise protocol, assigning the patient the more severe level of disability. Only patients capable of completing stage III of the treadmill exercise test (14 percent grade, 3.4 miles/hour) without dyspnea were assigned grade 0. Patients unable to complete Stage I (10 percent grade, 1.7 miles/hour) were assigned grade 3+. For patients whose condition was less easy to classify, we used data supplied by McDonough et al.[16] for normal middle-aged men and by Profant et al.[17] for normal middle-aged women, supplemented by our own unpublished data for younger patients.

Chest pain: 0 = none; 1+ = chest pain only at greater than ordinary activity, daily routine slightly compromised; 2+ = chest pain with ordinary activity, daily routine moderately compromised; and 3+ = chest pain with less than ordinary activity, daily routine severely compromised.

Syncope: 0 = none; 1+ = only one episode in the last year, daily routine slightly compromised (usually by anxiety); 2+ = more than one episode of syncope over the last year, daily routine moderately compromised; and 3+ = frequent or prolonged episodes of syncope, daily routine severely compromised. This symptom has an ominous connotation because of its known association with sudden death.

Presyncope (dizzy spells not related to other organ system disease): 0 = none; 1+ = dizzy spells with greater than usual activity or only transient orthostatic dizziness, daily routine slightly compromised; 2+ = dizzy spells with ordinary activity, daily routine moderately compromised; and 3+ = frequent dizzy spells occurring with less than ordinary activity, daily routine severely compromised.

Palpitations: 0 = none; 1+ = palpitations only with greater than ordinary activity, daily routine slightly compromised; 2+ = palpitations with ordinary activity, cardiac status moderately compromised; and 3+ = palpitations with less than usual activity or very frequent palpitations, or both, daily routine severely compromised.

Physical Findings, Electrocardiogram and Chest X-ray Film on Admission

Twenty-one of the 22 patients presented with a palpable apical presystolic impulse and all 22 patients had an audible atrial systolic gallop sound. Seven patients had a third heart sound gallop. A systolic ejection murmur was audible over the left precordium in all 22 patients, and the murmur was grade 3/6 or greater in intensity in 19 patients. Four patients had overt pulmonary congestion and five had peripheral edema. Nineteen patients had four or more points according to Romhilt and Estes'[18] electrocardiographic criteria for left ventricular enlargement. Two of the remaining three patients

TABLE I

Summary of 22 Patients

Case no.	Age, Race, Sex	Follow-up (yr)	TMI (yr)	Propranolol Dose (mg/day)	Symptom Scores* Dyspnea	Chest Pain	Syncope	Presyncope	Palpitations	Total Score	Functional Outflow Orifice† (cm^2)	Stimulated Gradient‡ (mm Hg)
1	35 WM	5.5	4	480	1/1	2/0	3/0	3/1	2/0	11/2	0.7/1.1	86/50
2	35 WM	7.5	4	480	2/0	2/1	1/0	0/1	0/0	5/2	2.6/NG	42/0
3	53 WM	5.5	5	320	1/1	0/0	3/0	3/1	1/0	8/2	1.3	135
4	23 WM	9	3	400	2/0	2/0	0/0	0/0	1/0	5/0	1.2/2.0	180/11
5	43 WM	6.5	3	480	2/1	3/1	0/0	1/0	1/0	7/2	2.0/NG	124/0
6	15 BF	3.5	1	400	2/0	0/0	0/0	0/0	3/0	5/0	1.9/2.1	90/30
7	56 BM	2.5	1	480	3/1	1/0	0/0	2/0	0/0	6/1	2.0	80
8	56 BF	3.5	2.5	480	3/2	1/0	0/0	2/0	2/1	8/3	0.6/0.6	180/110
9	34 BM	2.5	1	480	2/0	2/1	0/0	2/1	2/0	8/2	NG/NG	50/14
10	51 WF	2	1	480	2/0	1/0	0/0	2/0	0/0	5/0	1.3/0.5	178/125
11	57 WF	3.5	2	480	3/2	3/1	3/0	2/1	3/1	14/5	1.5/NG	94/28
12	33 BF	2.5	2	480	3/1	2/0	0/0	1/0	1/0	7/1	1.0/0.9	218/97
13	36 WM	2	1	640	2/2	3/1	0/0	2/2	3/1	10/6	1.8	110
14	61 WF	5	4	480	3/1	3/0	1/0	1/0	0/0	8/1	NG	90
15	57 WF	7.5	3	480	3/2	1/0	3/0	3/0	3/0	13/2	0.8/0.6	67/70
16	46 BM	4.5	1	240	1/0	2/0	0/0	0/0	0/0	3/0	2.2/NG	61/0
17	39 WM	5	3	640	3/2	2/0	0/0	1/0	1/1	7/3	0.6/1.8	192/46
18	34 BM	6.5	3	480	3/1	2/0	1/0	2/1	1/0	9/2	1.1/NG	120/0
19	51 WM	6	3	480	3/1	1/1	2/0	2/1	2/0	10/3	1.6/1.3	86/22
20	51 WM	4.5	3	480	2/1	2/0	2/0	2/1	0/0	8/2	0.7/1.4	122/78
21	54 WM	7.5	6	320	3/1	2/0	0/0	0/0	0/0	5/1	0.6	220
22	43 WF	8.5	4	480	3/1	3/0	2/0	3/1	1/0	12/2	NG/NG	30/0
	Mean	5.0	2.75	462	2.4/1.0	1.8/0.3	1.0/0	1.5/0.5	1.2/0.2	7.9/1.9	1.6/2.2	113/40
	SD	2.1	1.4	87	0.7/0.8	0.9/0.4	1.2/0	1.1/0.6	1.1/0.4	2.9/1.5	0.9/1.2	58/41
	P	...	...	...	<0.001	<0.001	<0.005	<0.001	<0.001	<0.001	<0.02	<0.001

* For each patient the first number is the initial symptom grade and the second is the grade at the time of this report.

† Resting subvalvular functional orifice as calculated with Gorlins' formula. NG = no gradient, functional orifice assumed to be 3.5 cm^2. Means and standard deviations reported are for the 17 patients who were restudied. The initial functional orifice for the entire group (22 patients) was 1.6 ± 0.9 cm^2.

‡ Means and standard deviations reported are for the 17 patients who were restudied. The initial stimulated gradient (mm Hg) for the entire group (22 patients) was 116 ± 55.

B = black; F = female; M = male; *P* = probability; SD = standard deviation; TMI = time to maximal improvement after the start of medical therapy; W = white.

had the Wolff-Parkinson-White syndrome, and one had complete left bundle branch block. Left atrial enlargement was disclosed on electrocardiography in 10 patients and suspected in 2 others. Six patients had Q waves suggestive of myocardial infarction.

The transverse diameter of the heart was evaluated with chest X-ray films taken at a standard distance of 6 feet by the method of Ungerleider and Clark.[19] The heart was considered enlarged if the diameter was greater than 10 percent above average. According to these criteria, the cardiac silhouette was normal in 10 patients and enlarged by 11 to 25 percent in 5 patients, 26 to 40 percent in 4 patients and more than 40 percent in 3 patients. Because the majority of patients entered our study before echocardiography was available to us, the effects of therapy on the serial echocardiogram cannot be assessed.

The diagnosis of hypertrophic obstructive cardiomyopathy was confirmed with classic findings at cardiac catheterization and angiocardiography in all patients.[20] Special attention was given to locating the catheter tip in the left ventricular inflow area to avoid false gradients produced by cavity obliteration.[21] Nineteen patients had a peak to peak pressure gradient at rest of 55 ± 32 mm Hg (mean ± standard deviation), and 3 had only a provocable gradient of 57 ± 25 mm Hg. Five patients had no mitral regurgitation. Seventeen patients had a regurgitant fraction ranging from a mere trace to 37 percent of total left ventricular output. Patients studied before 1970 did not have coronary arteriography. None of the 22 patients with important angina studied after that time have been found to have hemodynamically significant coronary obstruction.

Treatment (Propranolol)

Evaluation of heart rate response to propranolol with intravenous isoproterenol: Early in our study propranolol was administered four times daily at a unit dose of 10 or 20 mg that was increased gradually with no clear-cut end point. Significant improvement rarely occurred without a high degree of beta adrenergic blockade. We therefore evaluated heart rate response to a continuous infusion of isoproterenol at progressively increasing doses in 17 patients who were recatheterized to determine if heart rate response could be used as an index of beta blockade. The administration of intravenous isoproterenol can be hazardous because it can create an imbalance between myocardial oxygen supply and demand, particularly in the early unsteady state[22]; however, we observed no complications in our study group. Patients with significant angina or other evidence of myocardial ischemia were not challenged with isoproterenol before beta blockade, and the minute dose was increased gradually. The administration of 2.4 μg/min of isoproterenol produced near maximal beta stimulation, but increments in contractility,[23] cardiac output and outflow gradient sometimes occurred in the absence of a heart rate increase.

Oral dosage of propranolol: To block both the chronotropic and inotropic effects of beta stimulation consistently required daily doses of propranolol of 320 mg/day or greater. Thereafter, this was the minimal target dose. The dose was increased further if disabling symptoms persisted and no disturbing side effects occurred. Although larger patients generally require more propranolol than smaller ones, some small patients require large doses to control symptoms. We

now start with 40 mg four times a day while the patient is hospitalized, increasing the unit dose by increments of 20 mg at 24 to 48 hour intervals so that the desired beta blockade is achieved in a few days. Caution is exercised when the standing heart rate decreases to 60 beats/min. This approach is justified because of certain pharmacologic characteristics of propranolol: low bioavailability when administered orally because of a high hepatic extraction and binding to serum protein; a duration of action determined both by the size of the unit dose and by drug half-life; and the fact that toxicity does not appear to be related directly to the unit dose.[24] No major side effects have been observed using this program. The unit dose is now prescribed at meals and at bedtime to make compliance easier. Resting heart rate frequently increases gradually despite a constant dose of propranolol, probably because parasympathetic withdrawal causes the autonomic nervous system to regain its balance.

Additional therapy: Systemic hypertension, pulmonary congestion, peripheral edema and other conditions were managed as required. Pulmonary function was evaluated routinely so that noncardiac dyspnea could be identified and treated appropriately. Rhythm disturbances were treated if considered potentially lethal. Originally (in 1968) they were identified only with routine electrocardiography and treadmill exercise testing, but by 1975, both treadmill testing and 24 hour Holter monitoring were repeated at least annually. Symptom scores were reviewed at each clinic visit and medications adjusted. Each symptom was scored separately and a total score was recorded.

Data analysis: For this report, changes in symptoms and other important data were evaluated with Student's t test and other appropriate statistical methods for small samples. Data in the control group is partially incomplete because of the known limitations of retrospective studies. Less than optimal progress notes and the nonavailability of routine stress testing and Holter monitoring in earlier years prevented the accurate assessment of specific symptoms and the recognition of arrhythmias. For these reasons, the data on the control patients are discussed and compared with data on the protocol group at the end of the Results section.

Results

Protocol Group (Table I)

The protocol group consists of 14 men (mean age 42 years) and 8 women (mean age 47). The current age range is 15 to 61 years. The mean follow-up period is now 5 years, and the time for maximal improvement with medical therapy is 1 to 6 years (average 2.75). Thus, evaluation of results in less than 2 years may be misleading in some patients receiving medical therapy. The average dose of propranolol required for maximal control of symptoms was 462 mg/day, and the most common unit dose was 120 mg before meals and at bedtime.

Dyspnea: All 22 patients had some incapacity due to dyspnea at the onset of therapy. In 11 patients the dyspnea was severely incapacitating, in 8 moderate and in 3 mild. The mean initial dyspnea score for the group was 2.4, and the current score is 1.0 ($P < 0.001$). No patient's condition is worse and no patient remains severely limited. One patient (Patient 13) with moderate dyspnea has had no improvement. He has not complied with our medical regimen: He has missed many appointments, has failed to lose weight despite limiting obesity and has not attempted a prescribed exercise program. Six of the remaining 21 patients are now asymptomatic, 11 have mild dyspnea and 4 moderate dyspnea (Table I). Four patients have pulmonary dysfunction severe enough to contribute to effort dyspnea, but no patient has bronchial asthma. Patients 7, 12 and 17 have a moderate obstructive ventilatory defect. Patient 8 has a moderately severe restrictive ventilatory impairment with an obstructive component. All of these patients had severe dyspnea when they began therapy. No patient's condition has worsened despite large doses of propranolol, although two require oxtriphylline (Choledyl®) to control wheezing. Two patients now have moderate and two mild dyspnea. Patient 8 has severe outflow obstruction that has not decreased with the administration of propranolol; it is questionable whether cardiac surgery would decrease her moderate dyspnea, which is due at least in part to documented ventilatory impairment.

Chest pain: Twenty patients complained of chest pain before treatment. In 10 patients the pain was typical of angina pectoris, and in the other 10 it was atypical in one or more respects. Five of the patients with typical angina pectoris also had episodes of atypical pain. The incapacity due to chest pain was severe in 5 patients, moderate in 10 and mild in 5. Before therapy, the mean score for the entire group was 1.8; it is now 0.3 ($P < 0.001$). The condition of all patients is improved. Fourteen patients are free of pain, but 6 still have mild incapacity. Patients with typical and atypical chest pain had a similar degree of improvement.

Syncope: At the onset of therapy, 10 patients had recurrent syncopal episodes. In four patients the attacks were very frequent and severely disabling, in three they were moderately frequent and disabling and in three they occurred only occasionally. No patient now has syncope. In six patients, syncope was abolished solely by increasing the unit dose of propranolol. The relation between syncope and rhythm disturbances will be discussed later.

Presyncope: Seventeen patients had presyncope (recurrent dizzy spells). The attacks were frequent and severe in four patients, moderate in nine and only occasional in four. The initial mean score was 1.5 and the present score is 0.5 ($P < 0.001$). Eight patients are now asymptomatic, and eight have mild incapacity due to recurrent dizziness. Patient 13, who did not comply with our regimen, has shown no improvement and still has moderately frequent and disabling dizzy spells. No patient now has severely incapacitating presyncope. The relation between presyncope and rhythm disturbances will be discussed later.

Palpitations: Fifteen patients complained of recurrent palpitations, and in four patients the episodes were frequent and severely limiting. Four patients had moderate incapacity, and seven had only mild disability. The initial score for palpitations was 1.2 and the present score is 0.2 ($P < 0.001$). No patient is severely or moderately incapacitated now. Eleven patients have become asymptomatic, and four have infrequent attacks that cause little or no disability.

Potentially life-threatening arrhythmias (Table II): A potentially life-threatening arrhythmia was defined as (1) a supraventricular tachycardia that did not terminate spontaneously, its control requiring direct current cardioversion or continuous medication, or both, and (2) frequent ventricular premature complexes (more than 1/min or 30/hour). According to these criteria, potentially lethal arrhythmias were found in 11 of our 22 patients using routine electrocardiography, serial exercise stress testing and Holter monitoring. *All 3 patients without outflow obstruction* at rest but only 8 of the 18 patients with obstruction at rest were found to be at risk. Thus, the severity of rhythm disturbance is not directly related to the severity of subvalve obstruction. Some patients had more than one kind of potentially lethal arrhythmia. The spectrum of these arrhythmias is outlined in Table II. Only Patient 16, who had rhythm disturbance during physical effort, had frequent ventricular premature complexes without ventricular tachycardia or couplets. Patient 1 continued to have syncopal episodes despite antiarrhythmic therapy for recurrent ventricular tachycardia. Repeated Holter monitoring eventually documented an 18 second period of asystole as an additional responsible factor. A demand pacemaker was implanted with the pulse generator set at a slow rate so that it would not interfere with the sinus pacemaker when the spontaneous rate was adequate. The patient has now been free of syncope for 1 year. Patient 18 had recurrent syncope and underwent Holter monitoring on several occasions. He had only an occasional premature ventricular or premature atrial complex. During one monitoring period, a seizure was induced by voluntary hyperventilation. There was no rhythm disturbance at the time of the seizure, and subsequent diagnostic evaluation confirmed the presence of a primary seizure disorder.

In addition to 10 patients with frequent ventricular premature complexes, eight patients had less frequent ventricular extrasystoles. The severity of rhythm disturbance and the frequency of potentially lethal arrhythmias before the start of therapy is not known because an intensive search for rhythm disturbance was not undertaken until 1975. At that time, most patients were receiving large doses of propranolol, which in itself was responsible for control in four patients. The remaining seven patients required the addition of antiarrhythmic drugs.

Syncope, presyncope and palpitations were prominent in the majority of patients with rhythm disturbances but not in *all* patients with potentially lethal arrhythmias. The disappearance of syncope in four patients receiving large doses of propranolol before their first 24 hour electrocardiographic monitoring suggests that one or more patients may have been at risk in the past. For example, Patient 11 had Wolff-Parkinson-White syndrome and a history of recurrent and prolonged episodes of palpitations with dizziness and syncope before receiving propranolol, but no episodes of paroxysmal atrial tachycardia had been documented. When the patient's daily dose of propranolol reached 320 mg, the conduction abnormality and recurrent syncope disappeared, and the dizzy spells and palpitations became less severe.

TABLE II

Potentially Life-Threatening Arrhythmias in 11 of 22 Patients

	no. of Arrhythmias*
Frequent ventricular premature complexes	10
Ventricular tachycardia	4
>1 PVC/min with couplets	5
Frequent PVCs during exercise with ECG current of injury	1
Asystole	1
Paroxysmal atrial tachycardia associated with WPW	1
Paroxysmal atrial flutter	1

* Total of 13 is due to multiple arrhythmias in two patients.
ECG = electrocardiographic; PVC = premature ventricular complex; WPW = Wolff-Parkinson-White syndrome.

Management of other complicating conditions: Seven patients were found to have systemic hypertension that required diuretic drugs in addition to propranolol; one patient also required alpha methlydopa. The alleviation of symptoms in these patients did not differ from that in patients without hypertension. No patient now has elevated blood pressure. Digitalis was used at some time during the course of therapy in five patients whose symptoms worsened and then decreased when use of this drug was discontinued. In Patients 8, 15 and 17 pulmonary congestion with peripheral edema responded to diuretic drugs and progressively increasing doses of propranolol; in Patient 22 mild isolated pulmonary congestion responded to propranolol alone. Two patients had peripheral edema without signs of pulmonary congestion. In Patient 11 edema was controlled with diuretic therapy also used to control hypertension. Patient 20 required daily diuretic drugs for edema at the onset of therapy; however, his exercise tolerance improved with the administration of 480 mg/day of propranolol, and the diuretic drugs were discontinued.

Overall response to therapy: The average initial symptom score for the group of 22 patients was 7.9 (range 3 to 14). The average score is now 1.9, with a range of 0 to 6. Twenty patients have a score of 3 or less, and 18 of these are asymptomatic during their usual daily activities. No patient died or had a worsening of symptoms in the total follow-up period of 110 patient years. No patient now has atrial fibrillation, systemic or pulmonary thromboembolism, infectious endocarditis, pulmonary congestion or peripheral edema. The third sound gallop has disappeared in 4 of the 7 patients with this finding, but the fourth sound gallop persists in all 22 patients. Sixteen of the 19 patients with an ejection murmur of grade 3/6 or greater now have a murmur that is softer by one or two grades. The electrocardiogram of most patients changed little or not at all. However, left ventricular R wave voltage decreased in a few patients, signs of left atrial enlargement dis-

appeared in one patient, Q wave size decreased in three patients, and one patient with the Wolff-Parkinson-White syndrome now has a normal electrocardiogram. Assuming that a change of 10 percent or more in transverse cardiac diameter in the routine chest X-ray film is significant, heart size was unchanged in 13 patients, smaller in 7 and larger in 2. Although most of the changes in physical examination, electrocardiogram and X-ray examination indicate clinical improvement, no evidence was predictive. Moreover, both patients whose cardiac transverse diameter increased significantly are now asymptomatic during usual daily activities.

Hemodynamic data: There was no correlation between the initial degree of subvalve left ventricular obstruction and the initial total symptom score or between the degree of obstruction and the symptomatic response to therapy among the 17 patients who were recatheterized 1 year or longer after the start of treatment. In the analysis of subgroups, the chi square test revealed no difference in the response to therapy of patients with an obstructive orifice greater than or less than 1.5 cm^2. Although an analysis of paired differences revealed a significant increase in resting functional outflow orifice for the group of patients who were restudied (+0.6 cm^2, $P < 0.02$), all patients did not participate. Although Patient 10 had become asymptomatic, the obstruction was worse; however, Patients 8 and 15 had significant symptomatic improvement with no change in functional orifice (Table I). At least part of this discrepancy may be explained by the effect of beta blockade on the peak to peak gradient produced with isoproterenol or postextrasystolic potentiation (mean 113 mm Hg ± 58 in the first study and 41 mm Hg ± 40 in the second study, $P < 0.001$). The reduced response is documented further by a small but significant correlation between the total symptom score before and after treatment and the effect of beta stimulation on the peak to peak gradient ($r = 0.37$, $P < 0.05$).

Patients 8, 15 and 17 were offered surgery to relieve outflow obstruction but refused. More recently, Patient 17 underwent a second catheterization. His functional outflow orifice increased from 0.6 to 1.8 cm^2, thus suggesting that surgery might not have produced a greater alleviation of symptoms than that gained by the present medical program.

Control Group

Symptoms of 14 patients: The control group consisted of seven men with a mean age of 38 years and seven women with a mean age of 46 years. The age range at last follow-up was 17 to 78 years. Like the protocol group, these patients were followed up for a mean time of 5 years (range 2 to 13). When seen initially, 11 patients had some degree of exertional dyspnea and 10 had chest pain. Seven patients had recurrent dizzy spells and seven palpitations, but only two had syncope. The initial mean total score was 2.9 ± 1.3 compared with 7.9 ± 2.9 for the protocol group ($P < 0.001$). It is not clear whether the lesser severity of presenting symptoms among control patients means that they were actually less ill when first evaluated or whether the attempt to quantify their symptoms was less vigorous.

Results of treatment: Control patients were managed mostly with observation, but digitalis and diuretic and antiarrhythmic drugs were used in some. One patient who presented with mild dyspnea, chest pain and presyncope, became asymptomatic with the administration of reserpine and was lost to follow-up shortly after 2 years. The condition of the remaining 13 patients worsened, particularly in regard to dyspnea (from 0.9 ± 0.5 to 2.1 ± 1.0, $P < 0.001$). At the last evaluation the total symptom score for the group had increased significantly over the initial score to 5.4 ± 2.4 ($P < 0.001$) and was higher than that of the protocol group (1.9 ± 1.5, $P < 0.001$). In the control group the severity of dyspnea increased two to three grades in six patients and by one grade in five patients. Atrial fibrillation and progressive congestive failure developed in one of the six patients.

Four patients underwent myotomy-myectomy because of progressive symptoms. Their final score was computed preoperatively. Two of these patients (including the patient with atrial fibrillation) died in the immediate postoperative period. Of the 10 patients managed with medical therapy only, 4 died suddenly. Premature ventricular complexes had been identified in two of these patients on routine electrocardiography, and one patient was receiving quinidine at death. Thus, the overall mortality rate for the 14 control patients during a mean follow-up period of 5 years was 43 percent, or 40 percent if the four surgical cases are excluded. Five of the eight survivors are currently lost to follow-up, including the two survivors of myotomy-myectomy who were doing well when last seen in 1976 (9 and 6 years after operation). In two of the remaining three patients whose whereabouts are known propranolol therapy was instituted because of progressive disability during the last 18 months, and the condition of both is greatly improved.

Discussion

Aggressive propranolol therapy: the management of choice: The question whether a disease should be managed medically or surgically is probably answered best by comparing the natural history of the disease with the results of medical and surgical intervention. The anticipated annual mortality rate in patients with hypertrophic obstructive cardiomyopathy has been reported to be 3 to 4 percent,[2,8–10] but may in fact be higher, as indicated by the rate of almost 10 percent in our small group of nonrandomized control patients. The reported average surgical mortality rate for large series is approximately 14 percent,[3–7] but without aggressive medical management additional late deaths occur.[7] In contrast, none of the 22 patients in our medical protocol died during a mean follow-up period of 5 years while receiving an average dose of propranolol of 462 mg/day. Obstructive ventilatory impairment in the absence of true allergic bronchospasm was not a contraindication for the use of propranolol. Pulmonary function did not deteriorate in any patient.

All patients, including those with primary ventilatory impairment, have shown symptomatic improvement. The average rate of improvement is 58 percent for dyspnea, 83 percent for chest pain, 100 percent for syncope, 67 percent for presyncope and 83 percent for palpitations. The average rate of improvement in total score is 76 percent for the protocol group. In contrast, the symptoms of the control patients became 86 percent more severe, mainly because of a progression of dyspnea. The reported incidence rate of atrial fibrillation with progressive congestive heart failure is 8 to 10 percent,[2,20] and 1 of the 14 patients not treated with propranolol had this complication; however, all of our protocol patients continue to have sinus rhythm. Moreover, propranolol alone (one patient) or in conjunction with diuretic therapy is effective in relieving signs of congestive failure. We must therefore conclude that an aggressive medical program including large doses of propranolol is the best management for most patients with hypertrophic obstructive cardiomyopathy.

Optimal dosage and mechanisms of improvement with propranolol: We believe that earlier reports of initial impressive benefit with medical treatment followed by subsequent clinical deterioration[1–2,7] are related to inadequacy in the degree of beta blockade resulting from average daily doses of propranolol of less than 240 mg. It became evident as our study progressed that daily doses of propranolol of less than 320 mg were rarely effective and that larger doses were required for maximal benefit. The increments in dosage were determined empirically at first and later adjusted to obtain more complete beta blockade. Shand[25] has pointed out that the variability in dosage requirements is probably due to differences in beta receptor sensitivity, pharmacokinetic factors and severity of the underlying disease. Our results indicate that a higher level of beta blockade than previously recommended is required, but the mechanism for improvement is not completely explained by our data. Propranolol *does not* invariably reduce obstruction at rest, although it does reduce the increase in obstruction during beta stimulation. However, symptomatic improvement and the prevention of augmented obstruction with beta stimulation are not closely related. Because the degree of disability due to dyspnea, chest pain and syncope may be the same or even greater in patients with hypertrophic cardiomyopathy but without obstruction,[9] the obstructive component of the disease cannot be the only hemodynamic factor responsible for disability, nor is it necessarily the most important factor. Moreover, systolic ventricular performance is good except in a few patients in an advanced stage of the disease.

In contrast to aortic valve stenosis in which the flow pattern is symmetrical and the degree of obstruction constant, in hypertrophic obstructive cardiomyopathy the left ventricle empties earlier than is normal so that about 80 percent of the stroke volume has left the ventricle before obstruction, which is progressive, becomes maximal.[26] Obstruction does not prevent more rapid and more complete emptying than is found in normal ventricles.[27] This altered pattern of ejection occurs in patients with and without a pressure gradient[28] and therefore cannot be explained by the obstructive component of the disease.

Sudden death, syncope, arrhythmias and role of propranolol: Also common to the obstructive and nonobstructive form of hypertrophic cardiomyopathy is sudden death,[1–2,8–10,29] the most devastating complication and the most important factor in the reported annual mortality rate of 3 to 4 percent.[5] The clinicopathologic correlations of sudden death and electrical instability have been well described by James and Marshall[30] in a group of 22 subjects. Postmortem examination revealed abnormal fibrosis of the sinus node associated with or independent of narrowing of the sinus nodal artery in 12 of 22 hearts. Thirteen of the 22 hearts had conspicuous fragmentation of the body of the atrioventricular (A-V) node or His bundle. Significant narrowing of multiple small coronary arteries was found in the ventricular septum of 10 hearts, and deep clefts entering the endocardial surface into the septum were found in 7 other hearts. These findings are more than adequate to explain sudden death due to rhythm disturbance. Because there have been no fatalities in our 22 protocol patients despite a 50 percent incidence rate of potentially life-threatening arrhythmias, we suspect that large doses of propranolol alone may have been responsible for controlling lethal arrhythmias. Four of our 11 patients found to have potentially life-threatening arrhythmias now have only occasional premature ventricular complexes after therapy with progressively increasing doses of propranolol alone. Also, the frequency and severity of syncope, presyncope and palpitations decreased in some patients without the addition of antiarrhythmic drugs.

In contrast to our experience, Ingham et al.[31] reported that propranolol was not effective as an antiarrhythmic agent in patients with hypertrophic obstructive cardiomyopathy. However, no patient received more than 160 mg/day of propranolol, and the drug was not used in combination with other antiarrhythmic drugs, although propranolol is known to potentiate the antiarrhythmic effects of quinidine[32] and should have a similar effect in combination with drugs that have similar electrophysiologic effects. Their patients were not studied with Holter monitoring, and therefore the true incidence of rhythm disturbance in their patients is probably not known. The role of sympathetic neural activity in the genesis of ventricular arrhythmia has recently been emphasized by Lown et al.[33] It is likely that beta blocking agents act primarily by opposing sympathetic neural activity instead of acting directly on the myocardium. In regard to supraventricular tachycardias, Ingham et al.[34] performed electrophysiologic studies in a series of 13 patients with hypertrophic cardiomyopathy. Dual A-V nodal pathways were found in seven patients during control studies and provoked in three other patients with the intravenous administration of propranolol. They suggest that a dual A-V nodal response might account for the large incidence of supraventricular tachycardia in such patients and that propranolol might make things worse. However, the

frequency of paroxysmal atrial tachycardia did not increase in their group or in a similar group studied by Seides et al.[35] In all of our patients, *both* atrial and ventricular rhythm disturbances decreased significantly with the administration of propranolol alone or in combination with other antiarrhythmic agents. This finding was also reported by several other groups of investigators in patients with rhythm disturbance in general[36,37] as well as in patients with hypertrophic obstructive and nonobstructive cardiomyopathy.[38,39]

Mechanism of hemodynamic improvement with propranolol: The hemodynamic abnormality common to hypertrophic obstructive and nonobstructive cardiomyopathy is impairment of left ventricular filling due to massive hypertrophy. The isovolumetric relaxation time of the ventricle is prolonged,[40] and the early diastolic filling rate is reduced.[41] Moreover, difficulty in ventricular filling is increased by isoproterenol and reduced by beta blockade.[42] Because the rapid early diastolic filling phase is significantly impaired, filling depends to an unusual degree on vigorous atrial contraction. This may explain catastrophic clinical deterioration with death due to congestive heart failure after the onset of atrial fibrillation. Although we have no data to support the hypothesis, we suspect that improved diastolic compliance after propranolol therapy was responsible for the improvement in signs of congestive failure and dyspnea in our patients and for the prevention of atrial fibrillation.

Indications for surgery and long-term prognosis: We believe that the only *clear-cut* indication for surgical myotomy-myectomy is clinical deterioration in a patient with persistent severe outflow obstruction documented at recatheterization after aggressive prolonged medical management. Some patients with persistent severe obstruction and a personally unacceptable degree of disability may prefer surgical intervention. However, patients who are managed surgically still require management of diastolic compliance failure and control of potentially life-threatening arrhythmias. Despite our optimism about the results of long-term aggressive medical therapy, we must be cautiously optimistic regarding long-term prognosis. We have no evidence that our medical efforts changed the rate of progression of the underlying disease, and 5 years is a relatively short period in a patient's life.

Acknowledgment

We express our appreciation to Linda Attaway for secretarial assistance.

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Prolongation of Cardiac Conduction Times by Intravenous Aprindine in Man

H. LEON GREENE, MD, FACC
PHILIP R. REID, MD, FACC
ALLEN H. SCHAEFFER, MD

Baltimore, Maryland

The acute electrophysiologic effects of intravenous aprindine were evaluated in 48 patients to assess the effect on conduction times and refractoriness in patients with severe cardiac disease and arrhythmias. The patients had not responded to conventional antiarrhythmic medications or had been unable to tolerate effective doses of conventional medications because of side effects. Eleven patients had an abnormal H-V interval, 9 had prolonged QRS duration and 22 had evidence of severe left ventricular dysfunction. Aprindine prolonged conduction transiently in the atria, the atrioventricular (A-V) node, the His-Purkinje system and the ventricles. The refractory times of the atria, the A-V node and the ventricles increased insignificantly, both functionally and statistically. Atrioventricular block did not develop in any patient, and side effects were minor. Thus, aprindine can be safely administered intravenously (10 to 15 mg/min) to severely ill patients with arrhythmias that are refractory to other medications even in the presence of underlying conduction system and myocardial disease.

Aprindine hydrochloride, a new antiarrhythmic agent, has been used successfully to treat both ventricular and supraventricular arrhythmias[1–15] and is currently undergoing review for approval for use in the United States. Clinical studies have demonstrated that intravenous aprindine is useful in managing ventricular arrhythmias in patients with acute myocardial infarction.[13,16] Aprindine may be administered orally or intravenously, and its long half-life makes dosing necessary only every 8 to 12 hours. It is a tertiary amine, like many antiarrhythmic agents, and has electrophysiologic effects similar to those of quinidine and procainamide. As a tertiary amine aprindine undergoes N-dealkylation, but its major metabolic route appears to be inactivation by hepatic ring hydroxylation.

In the animal model aprindine increases refractoriness and slows conduction within the atria, the atrioventricular (A-V) node, the His-Purkinje system and the ventricles.[17–19] In Purkinje fibers aprindine decreases the maximal rate of rise of the action potential ($\dot{V}_{max}$) with a shortening of the action potential duration.[20–22]

The long-term cardiac electrophysiologic effects of oral aprindine in man have been reported.[1] The effective refractory periods of the atria and right ventricle increased, and conduction time increased in the A-V node, the His-Purkinje system and the ventricles. The short-term effects of aprindine are also important because of the increased intravenous use of this drug. The relatively few reports of its short-term electrophysiologic effects have dealt with small numbers of normal volunteers or patients with only mild impairment of left ventricular function or conduction. In these studies aprindine slowed conduction and impaired left ventricular function only slightly.[3,23–26]

From the Divisions of Cardiology and Clinical Pharmacology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland. This study was supported in part by Grants HL 18799 and 5P50 HL-17655 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received January 16, 1978; revised manuscript received April 18, 1978, accepted May 17, 1978.

Address for reprints: H. Leon Greene, MD, Blalock 530, The John Hopkins University School of Medicine, 601 North Broadway, Baltimore, Maryland 21205.

TABLE I

Summary of Data on 48 Patients Receiving Intravenous Aprindine

Diagnosis	Patients (no.)	Age (yr) (mean and range)	Sex (M/F)	VT/ SVT	MI (mean no. and range)	Survivors of "Sudden Death" (no.)
Coronary artery disease	25	61; 39–81	23/2	24/1	1.4; 0–5	10
Cardiomyopathy	10	41; 29–63	4/6	10/0	0	3
Wolff-Parkinson-White syndrome	6	46; 32–68	3/3	0/6	0.5; 0–2	0
Mitral valve prolapse	3	40; 21–51	1/2	3/0	0	1
Rheumatic heart disease	2	66; 55–76	0/2	0/2	0	0
A-V nodal reentrant tachycardia	2	58; 54–61	0/2	0/2	0	0

MI = myocardial infarction; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Our study evaluated the acute electrophysiologic effects of aprindine in 48 patients with cardiac arrhythmias; many of these patients had severely impaired conduction or depressed left ventricular function. The drug was administered intravenously in all patients for either refractory ventricular or supraventricular arrhythmias.

Material and Methods

All 48 patients were referred for investigational drug therapy because they had not responded to conventional medications. They had shown no improvement with other drugs (quinidine, procainamide, propranolol, phenytoin, digitalis and, in some instances, lidocaine, alone or in combination) or they had shown allergic or toxic side effects that made the continued administration of these drugs impossible. Thirty-seven patients had ventricular tachycardia, and 11 had supraventricular tachycardia. Their mean age was 54 years (range 21 to 81). Twenty-five patients had coronary artery disease, 10 a primary congestive cardiomyopathy, 3 mitral valve prolapse, 6 Wolff-Parkinson-White syndrome, 2 rheumatic heart disease and 2 A-V nodal reentry tachycardia. Fourteen patients had previously had a clinical cardiac arrest with ventricular fibrillation and had been resuscitated (Table I).

Electrophysiologic measurements: Informed consent was obtained from each patient for the use of aprindine and the electrophysiologic study. When possible, all cardioactive drugs were discontinued 48 hours before the electrophysiologic study. Patients were taken to the cardiac catheterization laboratory unsedated. Under 1 percent lidocaine local anesthesia, multipolar catheters were inserted in the usual manner in antecubital or femoral veins, or both.[27] Heparin was administered systemically. Catheters were positioned in the right atrium, right ventricle and at the level of the His bundle. Atrial and ventricular pacing were performed with 0.9 msec stimuli at twice diastolic threshold. Atrial and A-V nodal effective refractory periods were determined at a constant atrial pacing rate of 600 msec (S_1) by introduction of a premature atrial extrastimulus (S_2) every eighth beat.[28] The atrial effective refractory period was defined as the longest S_1-S_2 interval at which S_2 failed to capture the atria. The A-V nodal effective refractory period was defined as the longest A_1-A_2 interval that failed to produce an H_2. The ventricular effective refractory period was determined by introducing programmed single premature ventricular stimuli during atrial pacing at a constant rate of 700 msec. The ventricular effective refractory period was defined as the longest interval from the onset of the QRS complex to the ventricular stimulus that failed to capture the ventricle. Multiple surface electrocardiographic leads (usually seven: I, II, III, aVR, aVL, aVF and V_1) were recorded simultaneously. QRS and P wave widths were determined from the total duration of surface electrical activity in these simultaneously recorded leads. Intracardiac conduction times (high to low P wave duration, A-H and H-V interval) were measured from the earliest high frequency deflections in the respective intracavitary electrograms. The Q-T interval was likewise measured from the onset of the QRS complex to the end of the T wave in the multiple surface leads.

Aprindine administration: After refractory period studies, atrial pacing was discontinued, and aprindine was infused intravenously at a rate of 10 to 15 mg/min in an attempt to give a loading dose of 200 mg with frequent monitoring of the heart rate, blood pressure, spontaneous conduction intervals and symptoms. The mean dose was 189 mg (range 75 to 225). Four patients were given less than 200 mg because of their small body size (weight less than 55 kg) and the anticipated need for a smaller loading dose. Five patients were given less than 200 mg because of mild side effects. One patient was given a larger dose (225 mg) for better acute control of ventricular tachycardia. Spontaneous conduction intervals were measured and recorded at the end of infusion and 15 and 30 minutes later. Values reported are the maximal changes noted at any of these times, most commonly at the 15 minute interval. Refractory periods were measured 30 minutes after infusion of the drug was stopped. The mean serum aprindine level at this time was 1.25 μg/ml (range 0.40 to 3.35 μg/ml).

Ejection fraction: This was determined in 35 patients before aprindine infusion with single plane contrast left ventriculography (22 patients) or echocardiography or blood pool radioisotope scanning (13 patients). In 16 patients, left ventricular end-diastolic pressure was recorded before contrast angiography using fluid-filled catheters and Statham P23Db strain gauges.

Side effects: One patient had mild hypotension, one mild hypotension and nausea, one visual blurring, and two somnolence and slurred speech. All side effects were transient, lasting only 5 to 30 minutes.

Statistical methods: Data are expressed as the mean values ± standard deviation, and statistical significance was defined at the $P < 0.05$ level. Data were compared using Student's t test for paired and unpaired samples as appropriate.

Results

Ventricular function: In 10 patients a large left ventricular aneurysm precluded measurement of ejection fraction before administration of aprindine. Eight

TABLE II

Acute Electrophysiologic Effects of Intravenous Aprindine

	Before Aprindine*	After Aprindine*	Cases (no.)	*P*
Sinus cycle length	837 ± 176	832 ± 171	36	>0.8
Intraatrial conduction				
P wave duration	102 ± 16	143 ± 54	41	<0.001
High-low atrial conduction	29 ± 9	41 ± 12	32	<0.001
A-H at constant cycle length	113 ± 37	143 ± 54	39	<0.001
H-V	54 ± 14	67 ± 17	39	<0.001
QRS duration	93 ± 33	122 ± 43	45	<0.001
Q-T at constant cycle length	360 ± 36	388 ± 49	27	<0.01
Effective refractory period				
Atria	257 ± 42	271 ± 52	28	>0.1
Atrioventricular node	347 ± 81	368 ± 77	16	>0.1
Ventricles	276 ± 50	284 ± 52	25	>0.2

* All measurements in msec (mean ± standard deviation).
P = probability.

of these 10 patients also had severe diffuse hypokinesia or akinesia of the ventricular segments not involved in the aneurysm. Of the remaining 25 patients, 13 had an ejection fraction of less than 0.50, including 5 with a value of 0.30 or less (minimum = 0.20). Left ventricular end-diastolic pressure, recorded in 16 patients, was elevated in 9 (12 mm Hg or greater; maximum 26 mm Hg).

Electrophysiologic effects: Thirty minutes after the aprindine infusion, the mean (± standard deviation) spontaneous sinus cycle length was unchanged (837 ± 176 versus 832 ± 171 msec; no. = 36; difference not significant) (Table II). In 12 patients measurement of spontaneous sinus cycle length was precluded by atrial fibrillation, ventricular tachycardia with retrograde conduction, atrial flutter or a permanent pacemaker. In one patient with atrial flutter, the flutter cycle length increased from 250 to 345 msec.

The atrial effective refractory period prolonged only from 257 ± 42 to 271 ± 52 msec (no. = 28; difference not significant). However, intraatrial conduction time measured as P wave duration increased (102 ± 16 to 143 ± 54 msec; no. = 41; $P < 0.001$). Intraatrial conduction measured as high atrial to low atrial conduction time (time from the atrial deflection from the catheter at the superior vena cava-right atrial junction to the onset of atrial activity in the His bundle catheter) also prolonged (29 ± 9 to 41 ± 12 msec; no. = 32; $P < 0.001$).

Atrioventricular (A-V) nodal conduction time at an atrial paced cycle length of 600 msec increased with aprindine from 113 ± 37 to 143 ± 54 msec (no. = 39; $P < 0.001$). The A-V nodal effective refractory period, measured in 16 patients, was unchanged (347 ± 81 to 368 ± 77 msec; difference not significant). The atrial refractory period or atrial fibrillation or flutter precluded paired measurements before and after aprindine in the other patients.

His-Purkinje conduction time (H-V interval) increased with aprindine from 54 ± 14 to 67 ± 17 msec (no. = 39; $P < 0.001$), and the QRS complex widened transiently from 93 ± 33 to 122 ± 43 msec (no. = 45; $P < 0.001$). The maximal increase in H-V interval was 41 msec and in QRS duration was 132 msec. Eleven patients had an abnormal H-V interval (greater than 55 msec) before aprindine, the longest interval having a duration of 106 msec (119 msec after aprindine). In eight patients QRS duration was greater than 120 msec before aprindine, the longest duration being 192 msec (238 msec after aprindine). No patient had clinically significant A-V block with aprindine despite changes in the A-H and H-V intervals and QRS duration. No additional His-Purkinje block was elicited in any patient during atrial extrastimulation after aprindine. Patients with a prolonged H-V interval before aprindine did not have a greater absolute or percent increase in H-V interval after aprindine than patients with a normal H-V interval. Likewise, patients with a prolonged QRS duration before aprindine did not have a greater absolute or percent increase in QRS duration after aprindine than patients with normal QRS duration. The Q-T interval increased (from 360 ± 36 to 388 ± 49 msec; no. = 27; $P < 0.01$) at constant heart rate. Conduction intervals (A-H and H-V) and QRS duration returned to control values within 60 minutes of the end of infusion.

The effective refractory period of ventricular muscle did not increase significantly (276 ± 50 to 284 ± 52 msec; no. = 25; difference not significant). Among six patients with the Wolff-Parkinson-White syndrome, anterograde refractoriness of the accessory pathway was increased in two; retrograde refractoriness was increased in three of five of these patients (in one patient it was not adequately evaluated). The clinical results of many of these patients have been reported elsewhere.[2,29]

Discussion

Previous reports have documented the electrophysiologic response to long-term oral administration of aprindine in man[1–15,22] and the short-term electrophysiologic response in animals.[16–18] In these studies the refractoriness of atrial and ventricular muscle increased. In our short-term study in patients with uncontrolled arrhythmias, including many patients with conduction abnormalities and severe left ventricular

dysfunction, aprindine affected conduction times, whereas refractory periods were not significantly changed. Intraatrial, intranodal, His-Purkinje and intraventricular conduction times were all prolonged. However, no patient, even those with bundle branch block or H-V prolongation before infusion of aprindine, manifested clinically significant A-V block with aprindine. In this respect, aprindine appears to act like quinidine,[30] prolonging conduction reproducibly without causing A-V block. Our study demonstrated more profound effects on conduction than shown in previous intravenous aprindine studies,[24,26] perhaps because the dose was larger or the infusion more rapid or because conduction was more easily depressed in our patients as a result of intrinsic disease. Aprindine therefore is not absolutely contraindicated in patients with bundle branch or A-V block and refractory arrhythmias. Nevertheless, intravenous aprindine should be given carefully while monitoring the blood pressure and the QRS duration and A-V conduction in the surface electrocardiogram, and facilities should be available for emergency pacing in patients with conduction abnormalities before drug administration. The absence of A-V block in our patients does not preclude untoward results from intravenous infusion with other severely ill patients.

Acute versus chronic effects: The short-term effects of intravenous aprindine administration are slightly different from the long-term effects. Short-term administration of aprindine causes extensive myocardial binding[31] and may cause more rapid change in membrane sodium conductance and depression of rate of rise in the action potential. Electrophysiologic changes in man might be expected to be different in short- and long-term dosing. However, because this drug is being used acutely, particularly in patients with ventricular arrhythmias after myocardial infarction[13,16] and in some patients with conduction abnormalities, it is important to know both types of effects.

Therapeutic implications: Aprindine is a useful drug for treating ventricular and supraventricular arrhythmias. The electrophysiologic effects of both its intravenous and oral form are predictable. Its short-term side effects (hypotension, visual disturbances, paresthesias) are reversible and relatively minor; its long-term side effects (tremor, weakness) are more common, but are likewise reversible and related to the dose utilized and serum levels attained. There have been rare reports of agranulocytosis[32] and hepatic dysfunction in patients taking the drug chronically. Aprindine has been evaluated thus far in patients whose arrhythmias have been refractory to standard therapy. Its major advantage is its long half-life,[3] which reduces the need for frequent dosing. The risks of side effects must be weighed against the seriousness and intractability of the arrhythmia.

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Suppression of the Repetitive Ventricular Response: An Index Of Long-Term Antiarrhythmic Effectiveness of Aprindine for Ventricular Tachycardia in Man

ALLEN H. SCHAEFFER, MD
H. LEON GREENE, MD, FACC
PHILIP R. REID, MD, FACC

Baltimore, Maryland

The repetitive ventricular response, defined as the production of two or more ventricular premature complexes in response to a single ventricular pacing stimulus, is common in patients with serious ventricular arrhythmias. Twenty-seven patients with refractory ventricular tachycardia were studied to determine whether acute suppression of the repetitive ventricular response by aprindine predicts long-term effectiveness of this agent. Twenty-three of the 27 patients had the repetitive ventricular response before intravenous administration of aprindine, whereas only 6 had the response after aprindine. All patients were maintained on a regimen of oral aprindine and evaluated repeatedly for a mean of 12 months. Twenty of the 21 patients who had no repetitive ventricular response after intravenous aprindine manifested clinical improvement compared with only 1 of the 6 in whom the repetitive response was present after aprindine ($P < 0.0005$).

Aprindine is a useful agent in refractory ventricular tachycardia, and the absence of the repetitive ventricular response after its intravenous administration predicts long-term clinical responsiveness to the oral form.

Sudden cardiac death resulting from paroxysmal ventricular arrhythmias remains a major health problem in this country, accounting for as many as 400,000 to 600,000 deaths each year.[1–3] Despite the widespread use of antiarrhythmic agents, only beta adrenergic blocking agents have been shown to reduce the incidence of sudden cardiac death.[4,5] Unfortunately, the selection of an antiarrhythmic agent in the individual patient is often based on a trial and error process, in part because there is no short-term testing procedure for predicting long-term antiarrhythmic effectiveness.

The experimental production of a multiple or repetitive ventricular response after a single ventricular stimulus has been used as an index of ventricular electrical instability in animals and appears to be dependent on several factors, including stimulus intensity, stimulus pulse duration and relative degree of prematurity of the ventricular stimulus.[6–10] One study[10] suggests that the stimulus energy required to elicit a repetitive ventricular response bears a constant relation to the ventricular fibrillation threshold. Interventions altering the ventricular fibrillation threshold appear to correlate directly with the threshold required to produce a repetitive ventricular response.

Recently this technique has been safely adapted for use in man.[11–1 Several studies[15–19] have shown that a repetitive ventricular response occurs frequently in patients subject to recurrent ventricular arrhythmias. Although there have been differences in techniques, most studies have associated electrical instability with the ability to produce a repetitive ventricular response. In addition, a recent prospective study o

From the Department of Medicine, Divisions of Cardiology and Clinical Pharmacology, The Johns Hopkins University, School of Medicine, Baltimore, Maryland. This study was supported in part by Grants 5P50HL-17655 and HL18799 from the National Heart, Lung, and Blood Institute, The National Institutes of Health, Bethesda, Maryland. Manuscript received January 16, 1978; revised manuscript received July 5, 1978, accepted July 5, 1978.

Address for reprints: Allen H. Schaeffer, MD, Osler 503, The Johns Hopkins Hospital, 601 North Broadway, Baltimore, Maryland 21205.

TABLE I

Patient Population Before Treatment

Diagnosis	Patients (no.)	Age (yr) (mean; range)	Male/ Female Ratio	Myocardial Infarctions (mean)	Survivors of Sudden Death
Coronary artery disease	16	59; 39–77	15/1	2.1	5
Cardiomyopathy	9	42; 27–63	3/6	0	3
Mitral valve prolapse	1	21	0/1	0	0
Essential hypertension	1	56	1/0	0	1
Total	27	52; 21–77	19/8		9

patients surviving acute myocardial infarction demonstrated that the occurrence of a repetitive ventricular response was predictive of the development of symptomatic ventricular arrhythmias or sudden death.[20]

The present study was designed to evaluate whether suppression of a repetitive ventricular response by an antiarrhythmic agent (aprindine) predicts long-term clinical effectiveness of that agent.

Material and Methods

Patients: The study population consisted of 27 patients (Table I). All patients were referred specifically for evaluation and treatment of ventricular arrhythmias. In 22 patients the arrhythmias had proved refractory to treatment with conventional antiarrhythmic agents (quinidine or procainamide, or both; propranolol; phenytoin; digoxin; and in some instances intravenous lidocaine, alone or in combination); in 5 patients continued use of these agents was precluded by adverse or allergic side effects. All patients had previously documented episodes of symptomatic ventricular tachycardia, and nine had been successfully resuscitated from ventricular fibrillation. All patients who had electrophysiologic testing for the repetitive ventricular response before and after intravenous aprindine as described later and who had been evaluated for at least 9 months to determine the response to the drug (or until failure of the drug or death) are included in this report.

Electrophysiologic evaluation: After informed consent was obtained for electrophysiologic study and use of aprindine, all antiarrhythmic drugs were discontinued and a 24 to 48 hour drug elimination period was allowed before study. Patients underwent electrophysiologic study in the unsedated postabsorptive state. Multipolar electrode catheters were inserted with 1 percent lidocaine local anesthesia in an antecubital or femoral vein, or both, and positioned in the right atrium and right ventricle. Patients were then systemically anticoagulated with sodium heparin, 100 units/kg. Atrial pacing and ventricular pacing were accomplished with a programmable constant current stimulator using a square wave pacing stimulus of 0.9 msec duration at twice diastolic threshold but never greater than 4 milliamperes. The presence or absence of a repetitive ventricular response was determined while the right atrium was paced (A_1) at a constant cycle length of 700 msec. A single ventricular premature stimulus (V_1) was introduced every eighth beat, starting at the QRS complex and was progressively moved closer to the preceding T wave by 20 msec intervals until ventricular refractoriness or a repetitive ventricular response was elicited.

A repetitive ventricular response was defined as two or more ventricular beats in response to a single stimulus (V_1) that was reproducible with a stable catheter position free of mechanically induced ventricular beats (Fig. 1 and 2). A patient was considered not to have a repetitive ventricular response only if such a response were not consistently obtained in at least two separate ventricular sites. When a repetitive ventricular response was present, the right ventricular catheter was maintained in that position during the drug infusion and in subsequent repeat attempts to induce a repetitive ventricular response. No attempt was made to define a "zone" of premature ventricular stimuli in which repetitive ventricular responses occurred. Patients were classified simply on the basis of reproducible presence or absence of a repetitive ventricular response.

Aprindine administration: After evaluation for the presence of a repetitive ventricular response, atrial pacing was discontinued and aprindine infused intravenously at a rate of 10 to 15 mg/min with frequent monitoring of heart rate, blood pressure, QRS duration and symptoms. The mean dose

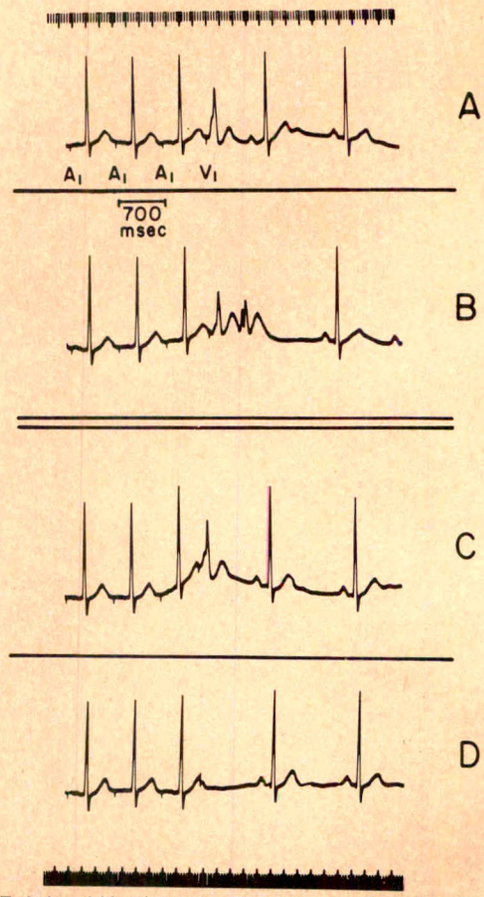


FIGURE 1. Lead V_5 electrocardiographic tracings from an electrophysiologic study of a patient whose repetitive ventricular response was suppressed by aprindine. **Upper panels** (before aprindine) illustrate the presence of the repetitive ventricular response. **A,** a single stimulus late in diastole results in a single ventricular response. **B,** a stimulus closer to the apex of the T wave results in two ventricular responses. **Lower panels** (after aprindine) demonstrate absence of the repetitive ventricular response. **C,** a single ventricular stimulus near the apex of the T wave results in a single ventricular response. **D,** a stimulus in the ventricular refractory period. A_1 = atrial pacing stimulus; V_1 = ventricular pacing stimulus.

administered was 193 mg (range 100 to 225). A 30 minute drug distribution period was permitted after the infusion was stopped and the patient was then reevaluated for presence of a repetitive ventricular response as described. Absence of this response before and after drug administration, by definition, meant that repetitive ventricular complexes could not be elicited at any stimulus interval in at least two right ventricular sites.

Clinical evaluation: After electrophysiologic evaluation, all 27 patients were given oral aprindine as the only antiarrhythmic agent using a mean dose of 119 mg/day (range 60 to 225) administered in divided doses two to three times a day. After discharge from the hospital, patients were evaluated at 1 to 4 week intervals with 24 hour ambulatory electrocardiographic recordings, serum aprindine levels and clinical assessment of response. Serum samples, run in duplicate, were obtained immediately before an expected dose for measurement of aprindine concentration (μg/ml of the hydrochloride salt) using gas-liquid chromatography.[21] The therapeutic range was considered to be 1.0 to 2.5 μg/ml.

Definition of clinical effectiveness: The clinical response was evaluated without knowledge of the electrophysiologic response. The criteria for a "good" clinical response were (1) more than 75 percent reduction of ventricular premature complexes or improvement in the Lown arrhythmia classification[22] (Table II), (2) reduction of clinical episodes of symptomatic arrhythmias, and (3) maintenance of therapeutic aprindine levels without use of additional antiarrhythmic agents.

TABLE II

Lown Arrhythmia Classification*

0 = No PVCs
I = <30 PVCs/hour, unifocal
II = >30 PVCs/hour unifocal
III = Multifocal PVCs
IVa = Couplets
IVb = Ventricular tachycardia/fibrillation

PVCs = premature ventricular complexes.
Adapted from Lown and Wolf.[22]

Data are expressed as mean values ± standard deviation. Data were compared using the Student's paired t test, the Student's t test for unpaired samples, or, where appropriate, Fisher's exact test for contingency.

Results

Electrophysiologic study: Twenty-three of the 27 patients (85 percent) had a repetitive ventricular response before the infusion of aprindine (Fig. 3); only 6 patients (22 percent) had this response after the infusion. There was no significant difference in the dose of intravenous aprindine given to patients whose repetitive ventricular response was abolished after aprindine (191 ± 26 mg) and the dose given to those in whom it remained (204 ± 9 mg).

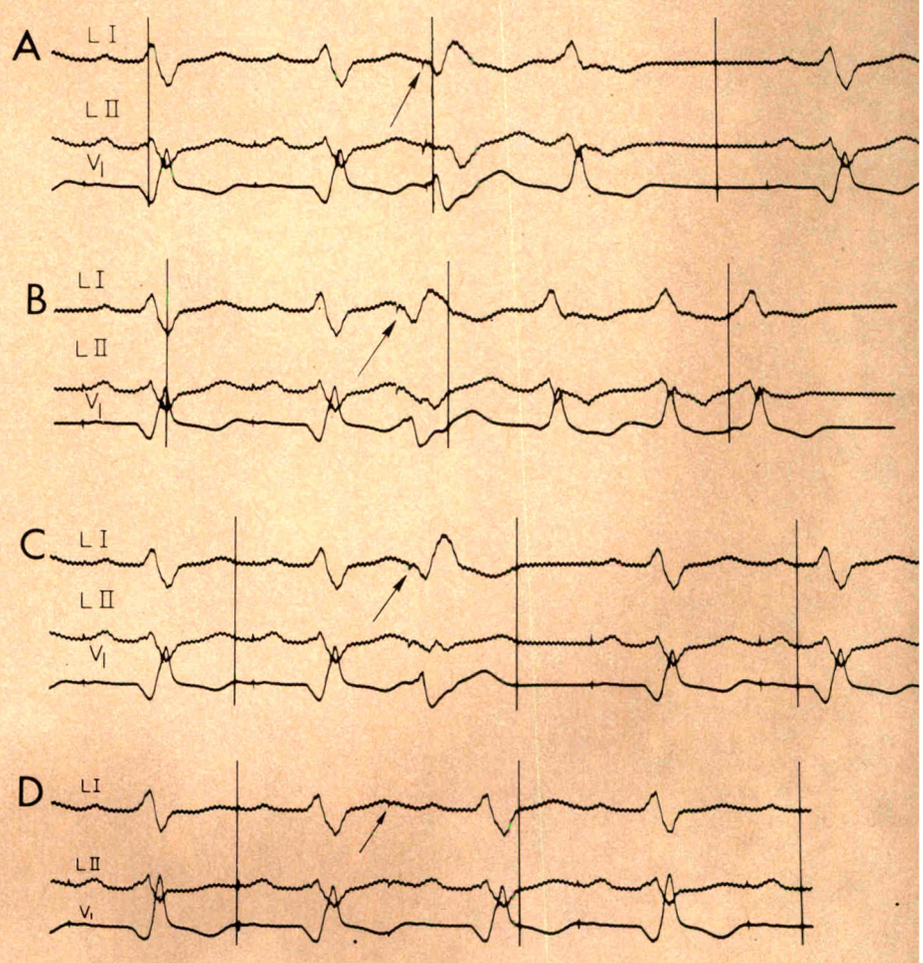


FIGURE 2. Multiple simultaneous electrocardiographic tracings (leads I, II and V_1) from a patient whose repetitive ventricular response was suppressed by aprindine. **Panel A** shows a single ventricular stimulus **(arrow)** followed by two ventricular premature complexes. When the stimulus was moved closer to the apex of the T wave **(panel B),** four ventricular premature complexes followed the stimulus. After aprindine **(panels C** and **D),** a single stimulus scanning diastole produced only one response up to ventricular refractoriness. Time lines are at 1.0 second intervals.

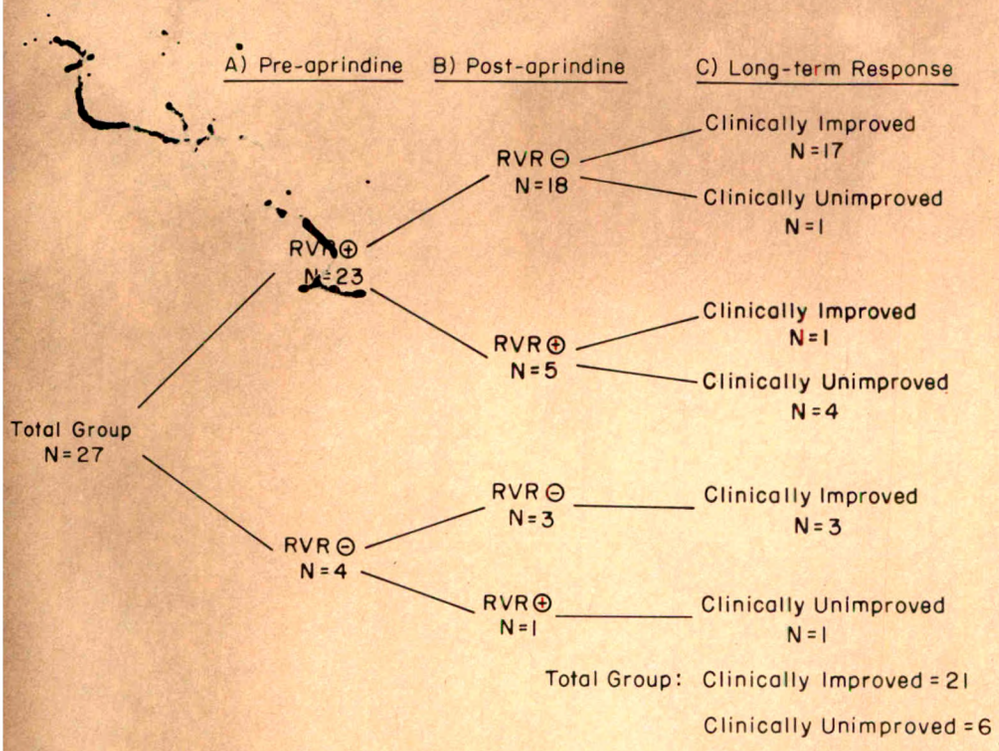


FIGURE 3. Schematic diagram summarizing results in the 27 patients. Patients are grouped according to the presence (+) or absence (−) of a repetitive ventricular response (RVR) before intravenous administration of aprindine. After aprindine, patients are again grouped on the basis of presence or absence of a repetitive ventricular response. They are then grouped according to whether or not they showed clinical improvement in the mean follow-up period of 1 year. N = number of patients.

Clinical evaluation: The mean evaluation period for these patients was 12 ± 7.3 months. A mean of 12 ambulatory monitoring records were obtained per patient. Twenty-one (78 percent) of the total group were judged to have a "good" clinical response (Fig. 3). Outpatient serum aprindine levels in those patients with a good response (2.1 ± 0.9 μg/ml) were not significantly different from those of patients whose condition did not improve (1.8 ± 0.4 μg/ml). Twenty of the 21 patients who had no repetitive ventricular response after intravenous aprindine had a good clinical response to oral aprindine compared with only 1 of the 6 patients in whom the repetitive ventricular response was present after aprindine ($P < 0.0005$). Figure 4 classifies the patients with and without a repetitive ventricular response after intravenous aprindine according to the most complex arrhythmia noted in any ambulatory monitoring record.

There were seven deaths among these 27 patients during the follow-up period. Four (15 percent) occurred suddenly and were believed to represent primary arrhythmic deaths. Three of these sudden deaths occurred in the group of 21 patients whose repetitive ventricular response was abolished after intravenous aprindine. These three patients had been asymptomatic on a regimen of oral aprindine for periods of 23, 18 and 9

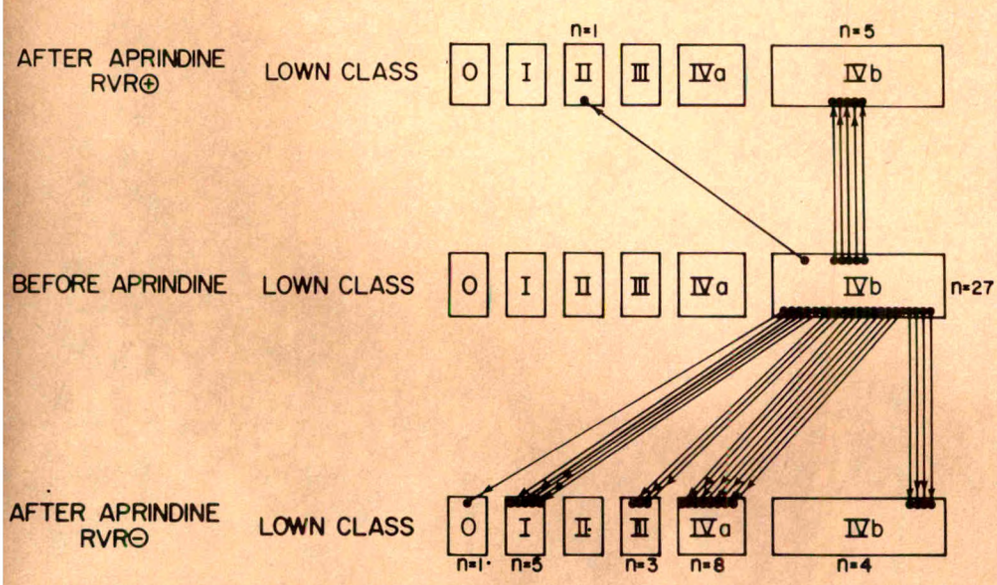


FIGURE 4. Diagram illustrating the response of patients to oral aprindine based on the most complex arrhythmia (Lown classification[22]) in any ambulatory monitoring record. Patients are grouped according to the presence (+) or absence (−) of a repetitive ventricular response (RVR) after intravenous administration of aprindine. N = number of patients.

months, respectively, with average serum levels of 1.8, 1.5 and 1.6 μg/ml. Serum drug levels obtained in two of these patients after cardiac arrest and a serum level obtained 2 weeks before death in the third patient were subtherapeutic (0.9, 0.8 and 0.9 μg/ml, respectively) for undetermined reasons. The fourth sudden death occurred in a patient in whom the repetitive ventricular response remained after administration of aprindine and occurred only 2 weeks after oral aprindine treatment was begun. This patient had an adequate serum aprindine level on the day before his death (2.3 μg/ml). The remaining three deaths were nonsudden; they occurred in two patients who died of refractory congestive failure and in one patient who died of sepsis complicating ventricular aneurysmectomy.

Discussion

Clinical usefulness of electrophysiologic testing for repetitive ventricular response: Our study demonstrates the usefulness of the electrophysiologic evaluation for the repetitive ventricular response. All 27 patients in this study had previously documented episodes of ventricular tachycardia, and 9 had survived sudden cardiac death requiring cardiopulmonary resuscitation. The persistence of these malignant ventricular arrhythmias at the time of referral for investigational drug therapy placed this group of patients at high risk[23,24] and emphasizes the need for rapid efficacious antiarrhythmic therapy. The selection of an antiarrhythmic agent that proves ineffective in a clinical evaluation period may expose the patient to potentially life-threatening arrhythmias. Acute suppression of the repetitive ventricular response by aprindine at the time of electrophysiologic study appears to be predictive of clinical responsiveness to long-term oral administration of aprindine. This phenomenon did not appear to be dose-related because there was no significant difference in the intravenous dose of aprindine given to those whose repetitive ventricular response was present and those in whom it was absent after aprindine. Clinical responsiveness to aprindine also did not appear to be dose-related because no significant difference was found between outpatient serum aprindine levels of patients with and without clinical improvement. However, maintenance of adequate serum levels may have been important in those whose condition improved because the three sudden deaths in the group whose repetitive ventricular responses were abolished with aprindine occurred in patients with a subtherapeutic serum level of aprindine.

In an earlier study from our laboratory the repetitive ventricular response was not found in 12 normal subjects without coronary artery disease or evidence of myocardial dysfunction at cardiac catheterization. In contrast, its occurrence in patients after myocardial infarction was found prospectively to identify patients who later had symptomatic ventricular arrhythmias or sudden death.[20] In the present study, the occurrence of the repetitive ventricular response in 23 of the 27 patients (85 percent) before the initiation of antiarrhythmic therapy is in agreement with previous data demonstrating the ability to elicit repetitive ventricular premature complexes during ventricular stimulation studies in patients with chronic ventricular arrhythmias.[15–18] Although some authors[17,15,25,26] have indicated that repetitive ventricular response occurs commonly, perhaps in normal subjects, their findings may be in part explained by differences in electrophysiologic technique.

The safety of programmed ventricular pacing has been established.[11–18] In a series of 340 patients undergoing electrophysiologic study in our laboratory there have been no deaths and only four episodes (1.2 percent) of ventricular arrhythmias resulting in hemodynamic compromise that required cardioversion or overdrive ventricular pacing. None of the patients in this study had arrhythmias requiring cardioversion during electrophysiologic study.

Clinical effectiveness of aprindine in preventing ventricular arrhythmia: The investigational antiarrhythmic agent used in this study was aprindine, which has been shown by our group and others to be useful in the management of both supraventricular and ventricular arrhythmias.[27–32] Aprindine is a tertiary amine like many other antiarrhythmic agents and has electrophysiolgic properties somewhat similar to those of quinidine and procainamide, and is thus in the type I antiarrhythmic category.[33] With oral administration its major effect appears to be prolongation of conduction and an increase of effective refractory periods in both atrial and ventricular muscle.[27] However, the exact mechanism of suppression of spontaneous arrhythmias is unknown. Aprindine can be administered safely both intravenously and orally with reversible side effects that are related to serum levels. The onset of action is within seconds of its intravenous administration; however, because it must be infused slowly (10 to 15 mg/minute or less), its peak effect occurs many minutes after onset of infusion, usually 10 to 15 minutes after the acute intravenous loading dose infusion has been completed. Its major advantage is its long half-life, which permits less frequent dosage and better patient compliance. Aprindine is metabolized primarily by the liver, and dose adjustments are necessary in patients with hepatic dysfunction or failure, impaired hepatic blood flow or poor cardiac output. In this group of 27 patients, all of whom had not responded to other antiarrhythmic agents, 21 (78 percent) had clinical improvement with aprindine on long-term follow-up.

Implications: Although this study evaluated response to the investigational agent aprindine, the use of the repetitive ventricular response may permit acute evaluation of effectiveness of other antiarrhythmic agents. This technique may permit immediate selection of an effective antiarrhythmic agent without exposing patients to the risk that malignant arrhythmias may develop during a trial and error evaluation period.

Acknowledgment

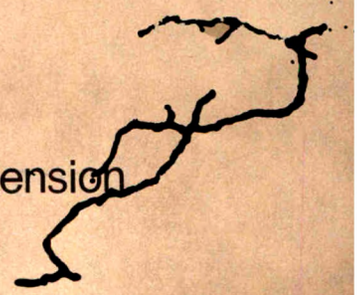
We express our appreciation to Ann Pendleton for organization of patient data, to Michaelene Llewellyn and Patricia Manspeaker for analysis of ambulatory electrocardiographic tapes, to Patricia Gongloff, Edwin Foster and Timothy Frazier for laboratory assistance and to Toni Haase and Barbara Pearce for secretarial assistance.

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Unilateral Stellate Block in the Treatment of Hypertension After Coronary Bypass Surgery

Implications of a New Therapeutic Approach



ROBERT C. TARAZI, MD, FACC
F. GEORGE ESTAFANOUS, MD, FACC
FETNAT M. FOUAD, MD

Cleveland, Ohio

Unilateral stellate ganglion block (right or left) was achieved by local injection of 15 ml of lidocaine in 27 patients with hypertension after coronary bypass surgery. The stellate block led to rapid and sustained control of blood pressure in 18 patients (9 of 15 with right stellate block and 9 of 12 with left stellate block). The reduction in arterial pressure was associated with significant ($P < 0.01$) reductions in total peripheral resistance and heart rate but no significant changes in cardiac output or central venous or left atrial pressures. This hemodynamic pattern as well as effectiveness of a unilateral approach suggests that the stellate block reduced arterial pressure by interrupting the afferent limb of a pressor reflex from the heart or great vessels, or both. The procedure was free from side effects and helped avoid prolonged parenteral administration of potent antihypertensive drugs.

Initial observations on hypertension after coronary bypass surgery[1,2] suggested to us that the increase in arterial pressure in the early hours after myocardial revascularization might be related to pressor reflexes originating from the heart or great vessels. Subsequent hemodynamic studies by Fouad et al.[3] lent support to that suggestion; the increase in arterial pressure after myocardial revascularization was shown to be associated with a generalized increase in total peripheral resistance with little or no change in cardiac output and no slowing of heart rate. This hemodynamic pattern was compatible with an increased sympathetic tone such as has been described by Brown et al.[4,5] and by Malliani et al.[5,6] after coronary distension.

An extensive body of animal experimentation has defined a number of potent pressor reflexes originating from the heart and great vessels; the initiating stimulus ranged from coronary distension[4–6] and myocardial ischemia[7,8] to the recently defined chemoreceptor hypertensive reflex.[9] Because our previous studies showed no obvious predilection of the hypertension occurring after bypass surgery to operations on any single coronary bed, and no apparent relation to ischemic episodes,[1,2] we thought that coronary or aortic pressor reflexes might be implicated. These reflexes involve sympathetic efferent fibers.[4–6,10] We therefore decided to try to control this hypertension with unilateral stellate blockade. Restricting the blockade to one side would prevent undue depression of cardiac performance[11]; further, the results, if successful, would favor the interpretation that a reflex was blunted or interrupted. More importantly from the therapeutic point of view, if a unilateral stellate infiltration successfully controlled this hypertension, the procedure would offer a useful alternative to the parenteral administration of antihypertensive agents now frequently used in this situation.[1,2,12]

From the Research Division and Department of Cardio-Thoracic Anesthesiology, The Cleveland Clinic Foundation, Cleveland, Ohio. This study was supported in part by Grant 6835 from the National Heart, Lung, and Blood Institute, The National Institutes of Health, Bethesda, Maryland; the John Hartford Foundation; and the Cleveland Clinic Foundation Research Projects Committee, Cleveland, Ohio. Manuscript received May 3, 1978; revised manuscript received July 11, 1978, accepted July 12, 1978.

Address for reprints: Robert C. Tarazi, MD, Research Division, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44106.

This report describes our experience with unilateral stellate ganglion blockade in treating 27 patients with hypertension. Control of blood pressure was obtained within 5 minutes of effective blockade in 18 of the 27 patients (67 percent).

Material and Methods

Patients

Twenty-seven patients (25 men and 2 women aged 33 to 68 years) were studied. There was no prior selection of patients; technical considerations dictated that only the first and second patients who manifested postoperative hypertension on the first and second days of each week could have repeated hemodynamic determinations. All patients in whom studies were technically possible were therefore investigated. The first step was a hemodynamic comparison of those who did and those who did not have hypertension after revascularization; this study has been described in detail elsewhere.[3] After this initial study, patients who had significant hypertension as defined previously[1–3] underwent unilateral stellate ganglion blockade, either right or left at random.

By chance, all patients in this study were normotensive preoperatively and none had evidence of significant reduction in ventricular function on history or on clinical and radiologic examination. Left ventricular end-diastolic pressure determined before ventriculography ranged from 6 to 26 mm Hg. Significant coronary obstructions were bypassed either with saphenous vein grafts or with left internal mammary artery anastomosis. Anesthetic technique, the agents used and postoperative management, identical in all patients, have previously been described in detail.[1,13]

Immediate postoperative monitoring: After return to the recovery room, the patients were kept sedated and adequately ventilated; both arterial and central venous pressures were continuously monitored. Arterial blood gases and pH, as well as serum electrolytes and hematocrit, were determined every 6 hours and any abnormality was corrected. All patients were artificially ventilated for the first 24 hours after surgery to maintain arterial oxygen tension between 100 and 150 mm Hg and arterial carbon dioxide tension between 30 and 35 mm Hg. Blood losses were estimated visually and the amount replaced as indicated by the patient's general condition as well as by changes in arterial and central venous pressures.

Intraarterial blood pressure, determined with use of cannulation of the right radial artery, was continuously monitored for the first 4 hours using a microtransducer. If the patient remained normotensive, arterial pressure was subsequently read at 15 minute intervals on the following day. The radial arterial cannula was usually removed after 24 hours and blood pressure levels were determined thereafter with auscultation. In all patients central venous pressure was measured every 15 minutes from a catheter introduced at operation through the internal jugular vein into the superior vena cava or right atrium. Left atrial pressure was available only in 12 patients who at operation had had a catheter placed into the left atrium at its junction with the superior pulmonary vein; readings of this pressure were also obtained every 15 minutes for 24 hours. Both venous catheters were left in place for 24 to 48 hours.

A hypertensive episode was defined as a sustained rise above preoperative levels of at least 20 mm Hg in diastolic blood pressure and 30 to 40 mm Hg in systolic pressure, provided that (1) this rise was not reversed by simple sedation, and (2) there was no evidence of hypoxia, hypercarbia, shivering, fighting the ventilator or intolerance of the endotracheal tube. We therefore included as hypertensive episodes only those instances in which the patient maintained a high blood pressure level for at least 10 to 20 minutes in spite of proper sedation.[1–3]

During the course of instructions preceding coronary arterial surgery, the purpose of the operation and its possible complications were explained to all patients. All were told that the more detailed hemodynamic evaluation in the early postoperative period would mean more determinations but no added arterial or other invasive procedure. Postoperative hypertension was mentioned to all as a possible postoperative complication; this hypertension would be controlled by drugs, or possibly blockade of a nerve (stellate infiltration) would be tried before drugs were administered. This procedure was submitted to and approved by the Institutional Review Committee (CRP 344).

Techniques

Hemodynamic study: After a 30 minute postoperative stabilization period, cardiac output was determined with the dye-dilution technique, using indocyanine green, in every patient. Continuous recording of arterial pressure helped early detection of hypertension. If the increase in arterial pressure had no obvious explanation and did not remit after sedation and adjustment of the respirator, cardiac output was then determined before the institution of antihypertensive therapy after blood pressure persisted at its higher level for at least 10

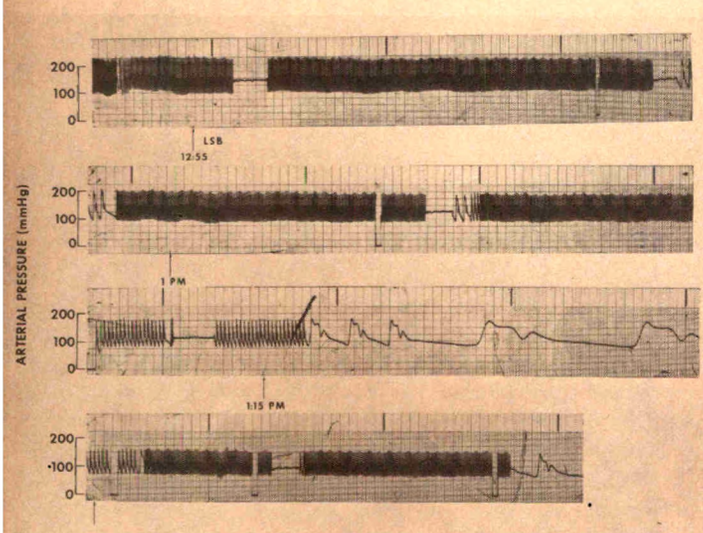


FIGURE 1. Continuous intraarterial recording before and after left stellate ganglion blockade. The pressure tracing was taken at different speeds to ensure that lower pressure levels were not due to damped pulsation. Mean arterial pressure was also recorded at various intervals. The time elapsed from stellate blockade (12:55 PM) to normalization of blood pressure (1:19 PM) is recorded immediately below each strip. Skin temperature (TEMP.) refers to the temperature recorded over the left index finger to determine the effectiveness of stellate blockade.

TABLE I

Control of Hypertension by Unilateral Stellate Blockade: Hemodynamic Response in 18 Patients (mean ± standard error of the mean)

	Right Stellate Blockade (no. = 9)			Left Stellate Blockade (no. = 9)		
	Before	After	P*	Before	After	P*
SBP	168 ± 5.5	119 ± 3.9	<0.001	185 ± 6.1	139 ± 6.4	<0.001
DBP	99 ± 2.8	75 ± 2.2	<0.001	98 ± 2.7	73 ± 2.9	<0.001
HR	94 ± 4.9	87 ± 5.1	<0.001	96 ± 5.8	88 ± 5.5	<0.01
CO	4.01 ± 0.4	3.49 ± 0.4	NS	4.12 ± 0.4	3.91 ± 0.4	NS
SI	22 ± 2.6	21 ± 2.8	NS	23 ± 2.4	24 ± 2.3	NS
TPR	66 ± 8.5	53 ± 6.4	<0.01	62 ± 4.1	49 ± 3.1	<0.025
CVP	9.2 ± 1.0	8.9 ± 1.1	NS	9.4 ± 1.3	9.6 ± 1.2	NS
LAP	14.5 ± 2.0	12.3 ± 2.6	NS	14.4 ± 1.4	14.2 ± 1.3	NS

* *P* (probability) value refers to statistical significance of paired *t* test.
CO = cardiac output (liters/min); CVP = central venous pressure (cm saline solution); DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats/min); LAP = left atrial pressure (cm saline solution); NS = not significant; SBP = systolic blood pressure (mm Hg); SI = stroke index (ml/m^2); TPR = total peripheral resistance (units·m^2).

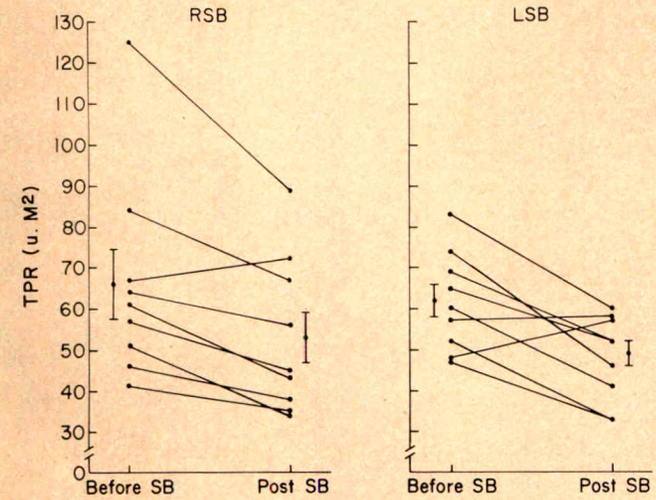


FIGURE 2. Change in total peripheral resistance (TPR) in response to unilateral stellate ganglion blockade (SB)—right stellate blockade (RSB) in the **left panel** and left stellate blockade (LSB) in the **right panel.** In all but 2 of the 27 patients, total peripheral resistance was reduced by the stellate blockade; in 1 patient resistance was practically unchanged (47 to 48 units) after left stellate blockade. The **bars** at extremes in both panels illustrate mean ± 1 standard error. The reduction in resistance was significant ($P < 0.01$ for right and $P < 0.025$ for left stellate blockade).

to 20 minutes. Output was determined in triplicate with the dye-dilution technique (indocyanine green); 1 ml of the dye solution (5 mg/ml) was flushed as a bolus dose in the superior vena cava by way of the catheter introduced at operation through the right jugular vein. Arterial blood was withdrawn from the right radial artery after each output determination, and the blood withdrawn was immediately reinfused to avoid blood loss, as described in detail previously.[3,14] Cardiac output was determined when hypertension was established, then again at 5, 10, 20 and 30 minutes after the unilateral stellate ganglion blockade. Cardiac output was calculated with the Hamilton-Stewart technique, and derived variables were calculated using standard methods.[14] For determination of ejection time, arterial pressure was recorded at a paper speed of 100 mm/sec; the values reported were an average of values from at least 5 to 10 beats. Values reported are those obtained when arterial pressure stabilized at its new level after a demonstrably effective stellate ganglion blockade.

Stellate ganglion blockade: Either the right or left stellate ganglion was infiltrated with lidocaine (15 ml of 2 percent solution) using a paratracheal approach at the level of the Chassaignac's tubercle (C_6).[15] Choice of the side of infiltration was random, 15 patients had effective right stellate blockade and 12 had effective left stellate blockade. In no case were both ganglia infiltrated in the same patient.

Effectiveness of the stellate blockade was determined by monitoring the skin temperature changes on the forearm and hand on the side of the blockade. It was not thought possible in the postoperative setting to depend with confidence on changes in forearm color or in facial sweating or the recognition of a Horner's syndrome. Temperature was measured at three localized points: over the forearm and thenar eminence and on the tip of the index finger. An increase of skin temperature by at least 5° F was required to consider a blockade effective.[16]

If an effective stellate blockade failed to control blood pressure within 30 minutes, therapy with nitroprusside was instituted. During and after the stellate blockade, the patients were carefully monitored for signs of diminished cardiac performance. Particular care was paid to changes in heart rate and rhythm as well as to central venous and left atrial pressures. No patient had serious bradycardia (heart rate less than 60 beats/min) or an increase in central venous or left atrial pressure of more than 1 to 2 cm saline solution.

Tests of statistical significance were calculated with standard methods[17]; results were considered significant when the probability (P) value was <0.01 and of questionable significance when it was <0.05.

Results

Effect on blood pressure: Stellate ganglion blockade was attempted in 29 patients; in 27 the procedure was successful, as shown by a remarkable increase in skin temperature of the ipsilateral forearm and hand (at least 5° F, but mostly 10° F). The two patients in whom the infiltration apparently did not block the stellate ganglion (neither had a change in skin temperature) were not included in the study. In 18 of the 27 patients with successful stellate infiltration, the unilateral block led to a rapid (within 5 to 10 minutes) reduction of blood pressure to normal, near normal or even less than normal levels (Fig. 1). Subsequently the blood pressure remained well controlled for the whole follow-up period in coronary care. In no instance did we

TAB[illegible]

Pers[illegible] hypertension Despite Effective Stellate Blockade: Hemodynamic Effects in Nine Patients (mean ± 1 standard error of the mean)

	Right Stellate Blockade (no. = 6)		Left Stellate Blockade (no. = 3)	
	Before	After	Before	After
SBP	171 ± 7.8	163 ± 7.2	187 ± 6.4	172 ± 3.3
DBP	107 ± 2.6	102 ± 2.3	93 ± 3.3	93 ± 6.7
HR	97 ± [illegible]	89 ± 3.5*	94 ± 5.2	93 ± 4.4
CO	4.82 ± 0.5	4.26 ± 0.6	4.83 ± 0.2	4.37 ± 0.3
SI	29 ± 3.4	28 ± 4.2	25 ± 0.6	23 ± 1.7
TPR	49 ± 6.4	61 ± 15.4	53 ± 4.5	56 ± 3.4
CVP	9.2 ± 1.4	8.1 ± 1.7*	8.7 ± 0.7	8.5 ± 0.5
LAP	12.6 ± 0.2	11.1 ± 0.6	. . .	. . .

* Apart from this difference ($P < 0.05$) none of the other differences recorded was statistically significant.
Abbreviations as in Table I.

encounter a complication related to the stellate blockade itself or a disturbance in cardiac rate or rhythm even in those whose blood pressure was not reduced. There was no significant difference in effectiveness of blood pressure control between right and left stellate ganglion blockade; arterial pressure was reduced in 9 of 15 patients with right stellate blockade and in 9 of 12 with blockade of the left side (chi square = 0.18; difference not significant).

Other cardiovascular effects: The reduction in blood pressure in response to either right or left stellate ganglion blockade was associated with a significant diminution in total peripheral resistance (Table I, Fig. 2), whereas cardiac output did not change significantly. In all 27 patients, the stellate blockade resulted in some slowing of heart rate. This slowing was highly significant in patients whose blood pressure decreased after either right or left stellate blockade (Table I). The slowing was statistically less significant among nonresponders, possibly because of the smaller number of patients in this group (Table II). Lack of arterial pressure response to effective right or left stellate ganglion blockade was not associated with a significant change in other hemodynamic indexes (Table II). In particular, there was no evidence of depressed cardiac performance in the patients studied. Central venous pressure was determined in all 27 patients; left atrial pressure was recorded in only 12 patients (7 of 15 with right stellate blockade and 5 of 12 with left stellate blockade).

Discussion

Mechanisms of blood pressure reduction by stellate blockade: Effective unilateral stellate ganglion blockade (either right or left) effectively controlled hypertension after myocardial revascularization in the majority (18 of 27) of our patients. The reduction in blood pressure was rapid, smooth and related to a decrease in peripheral resistance (Fig. 2) with no evidence of diminished cardiac performance (Tables I and II). These results were taken to suggest that control of blood pressure by stellate blockade was most probably due to interruption of afferent fibers coursing in or relaying through either stellate ganglion. This interpretation is based on inferential rather than on direct evidence, which would be difficult to obtain in man. Although incontrovertible proof may not be available, there are many reasons supporting the suggestion that unilateral stellate blockade controlled this form of hypertension mainly by interrupting the afferent limb of a pressor reflex.

Of particular importance is the lack of change in cardiac output after effective unilateral stellate infiltration (Table I). If the blockade had acted mainly by interfering with efferent cardiac sympathetic drive, one would expect a depression of cardiac output.[18] This is what has repeatedly been reported with acute beta adrenergic blockade[19–21]; cardiac output is significantly reduced with no change in arterial pressure because of a compensatory increase in total peripheral resistance. This response to interference with adrenergic influences on the heart is in marked contrast with the hemodynamic effects of unilateral stellate blockade. In our study, cardiac output was unaltered irrespective of the effect of blockade on arterial pressure (Tables I and II); control of the hypertensive crisis was associated with a significant reduction in total peripheral resistance irrespective of the side infiltrated (Fig. 2).

The efficacy of right stellate ganglion blockade also suggests that control of hypertension was not the result of diminished myocardial contractility, because that ganglion has more of a chronotropic than an inotropic influence on the heart.[22] After right stellate blockade, heart rate was slowed in all patients, presumably as a result of interference with efferent fibers, whereas arterial pressure was reduced in only 9 of 15 patients. This dissociation between heart rate and blood pressure responses to the stellate blockade also suggests that interference with efferent fibers only is not sufficient to account by itself for the control of this hypertension. This suggestion is further supported by the effectiveness of a unilateral stellate blockade in controlling the increase in arterial pressure.

Role of "cardiogenic hypertension": The importance of pressor reflexes originating from the heart and great vessels has been repeatedly demonstrated by the work of Brown, Malliani, Peterson, James and their

associates.[4–10] Malliani and Brown[7] demonstrated that depressor reflexes originating from the coronary arteries were mediated by vagal afferents in contrast to pressor reflexes that coursed through sympathetic afferents. A hypertensive chemoreflex from the heart was related by James et al.[9] to a small serotonin-sensitive chemoreceptor in an area whose blood supply was derived from a special small branch of the left main coronary artery. Malliani et al.[23] reported that stretch of the thoracic aorta in cats led to reflex increases (mediated by sympathetic afferents) of arterial pressure and heart rate.

It is apparent, therefore, that the role of the heart in hypertension may not be limited to conditions with increased cardiac output.[24] Reflexes originating from the heart or great vessels may play an active role in the initiation of some types of the disease. "Cardiogenic hypertension"[24] has been suggested as a possibility from both clinical observations[1,25] and animal experiments[4–10]; our study may be the first to provide evidence of its occurrence in man and of the possibility of control of some forms with unilateral stellate ganglion blockade. Reports of increased plasma renin activity and catecholamines in association with hypertension after myocardial revascularization[26] do not necessarily contradict this hypothesis. Sympathetic stimulation is a potent cause of renin release[27]; if past experience with hypertension research is any clue, this form of hypertension will probably demonstrate a multifaceted aspect.[28]

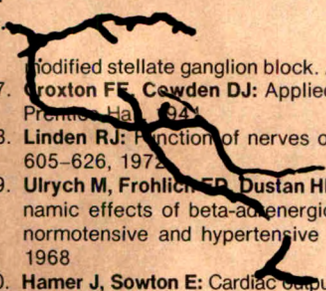
Clinical factors precipitating or predisposing to hypertension after coronary bypass surgery: The evidence is mostly negative concerning the particular stimulus responsible for the hypertension after coronary bypass surgery. Neither the incidence of hypertension nor its control by stellate blockade was related to myocardial infarction. No patient described in this or previous[1] series had a myocardial infarction after surgery, as evaluated by clinical findings or serum enzyme and electrocardiographic changes. Again, neither the incidence of hypertension[1,2] nor the degree of success of the stellate blockade was related to the artery grafted. There was no difference in incidence of hypertension either in our initial study or in this series between right or left coronary bypass. If the serotonin-sensitive chemoreceptor is found only in the vicinity of the proximal part of the left coronary artery, one might conclude that it may not play an important role in this type of hypertension. Further, this reflex is mediated by vagal afferents,[9,29] and more studies are needed to prove its occurrence in man.

One could think of an alternate possible mechanism for this paroxysmal hypertension, namely the inactivation of a depressor reflex rather than the activation of a pressor one. Should surgery interrupt some nerve fibers that act reflexly to restrain sympathetic activity, then the postoperative hypertension might be the result of deafferentation of this reflex. However, this view is purely speculative and our results, as well as the previous work of Liard et al.[30] on stellate ganglion stimulation in conscious dogs, do not support such a hypothesis.

Advantages of stellate blockade. Whatever the origin of the presumed reflex, stellate ganglion blockade proved to be a reliable and safe maneuver. Blood pressure was controlled rapidly and hypertension did not recur; both the patient and nursing staff were spared the difficulties of continuous nitroprusside infusion. Another advantage was the avoidance after open heart surgery of complex procedures such as epidural anesthesia, that were suggested for the control of this hypertension.[31] Stellate ganglion infiltration requires careful training and expertise to avoid possible complications,[11] and bilateral blockade is not recommended. However, unilateral stellate blockade offers a possible alternative to the administration of parenteral antihypertensive agents for the treatment of hypertension after myocardial revascularization. It may help to avoid some of their difficulties and side effects.[12]

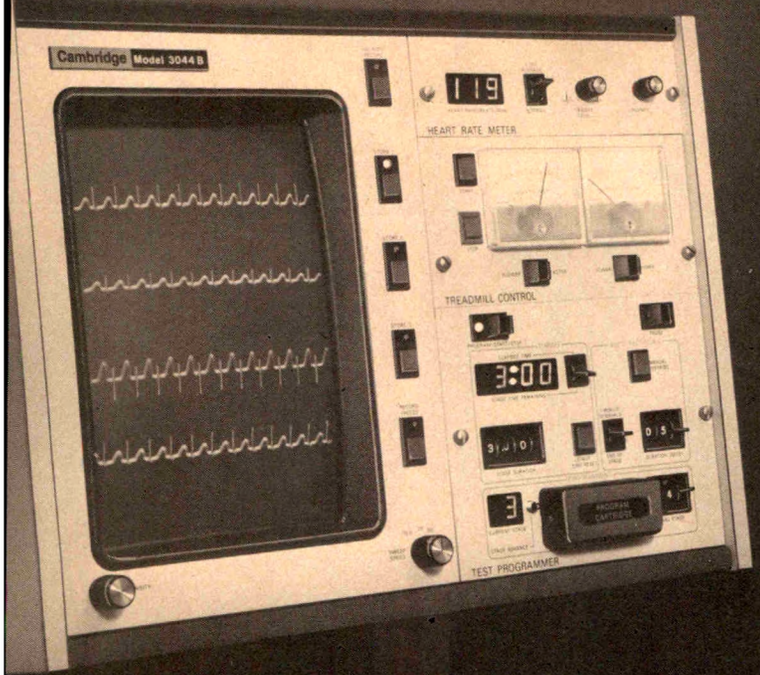
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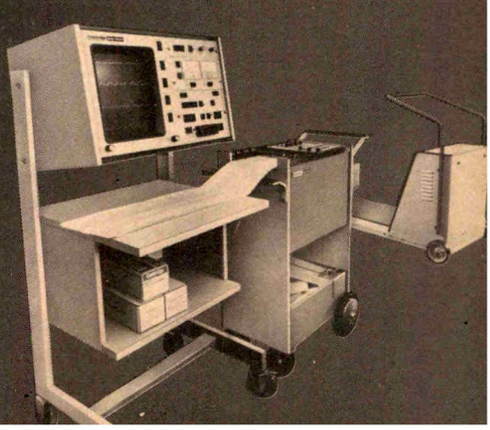
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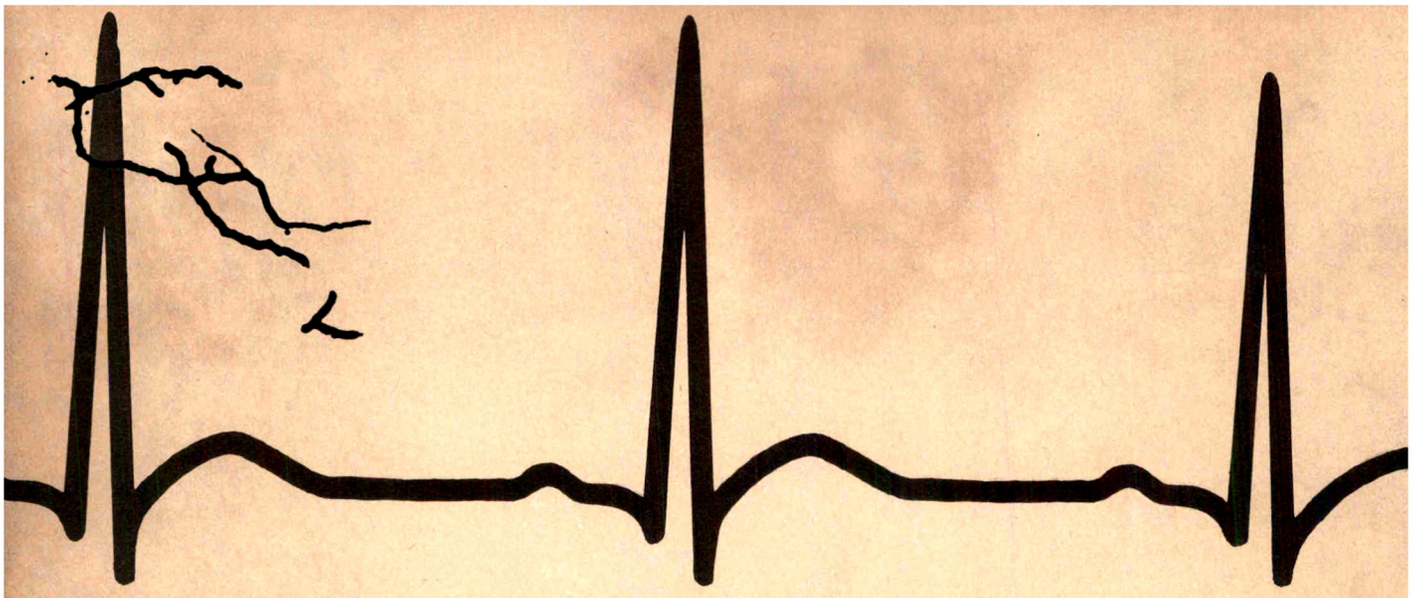
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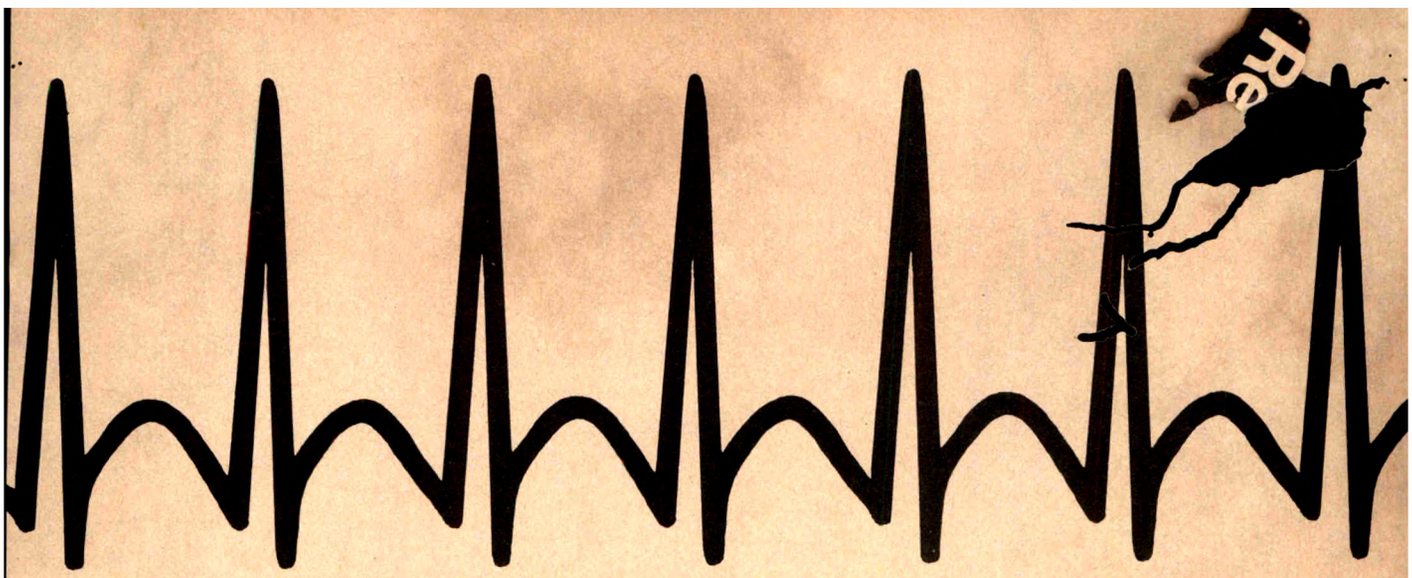
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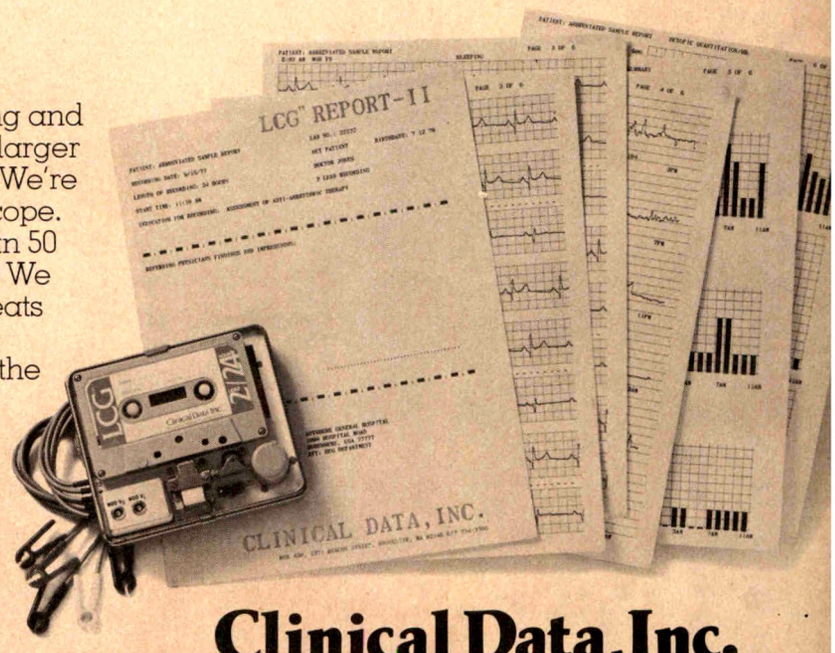
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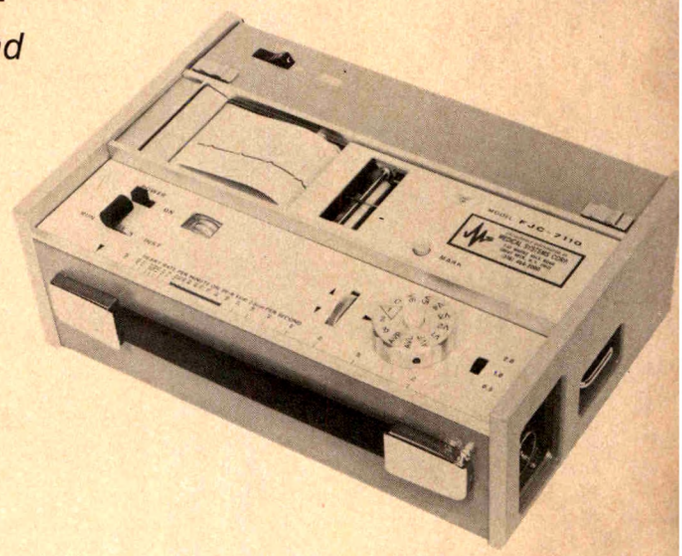
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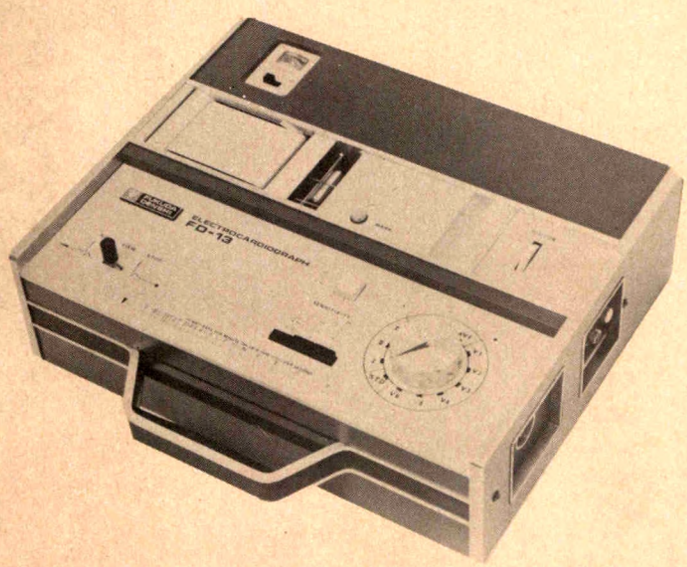
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*Based on actual case history (photos posed by professional model).

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- convenient dosage schedule that's easy to remember: 1 to 2 Dura-Tabs® every 8 or 12 hours
- h.s. dose helps avoid early morning reversion

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.

Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

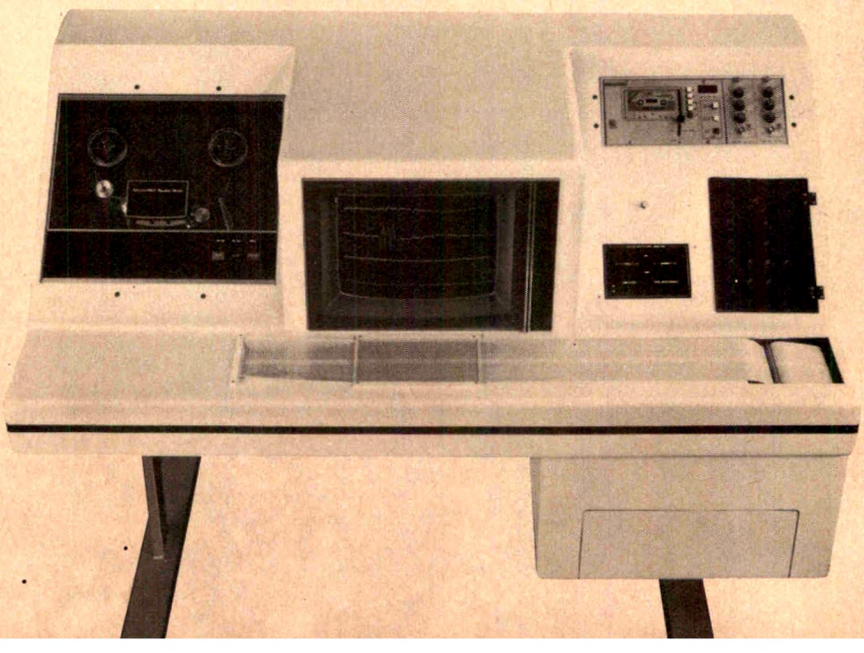
It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances. 101-71

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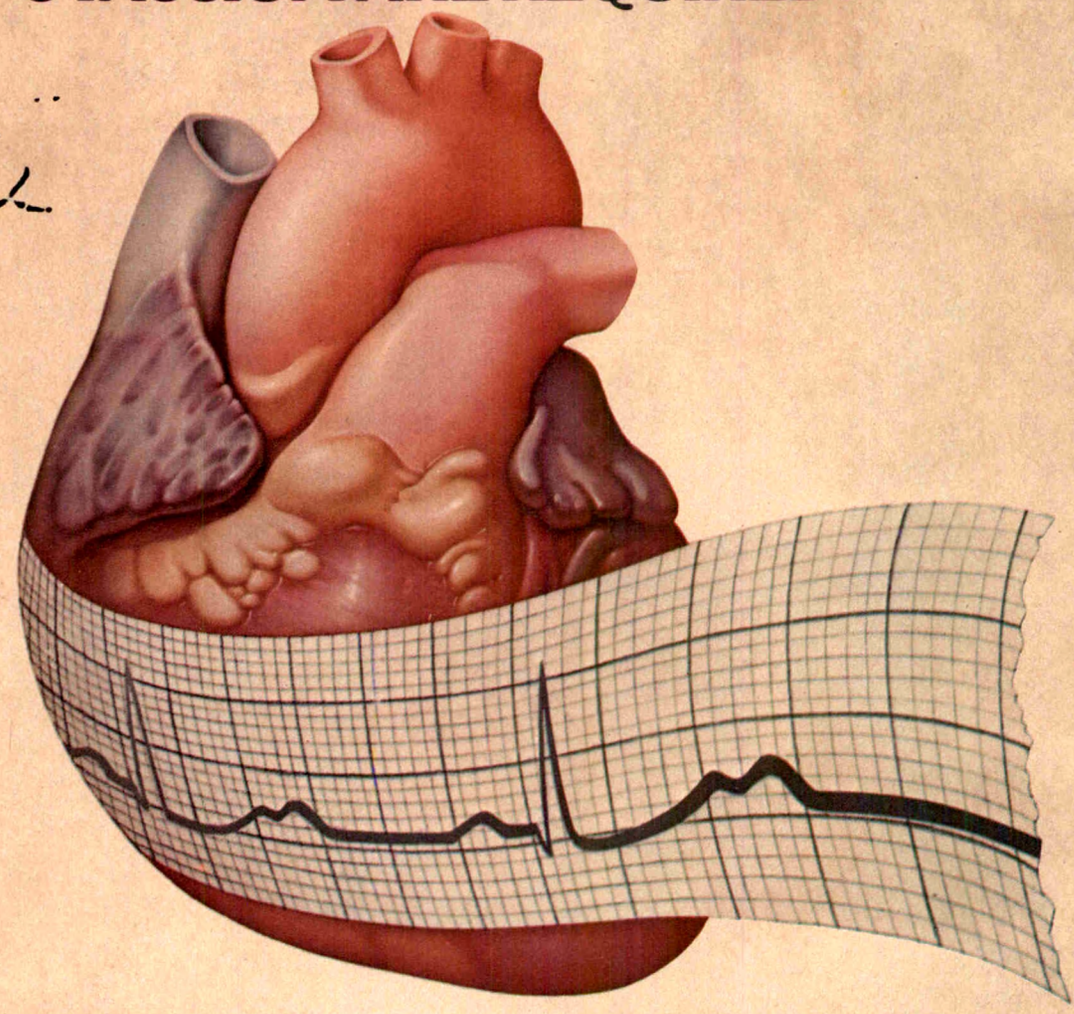
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40 mEq per 15 ml

Indications: KAON-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. KAON-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: In patients with hyperkalemia, chronic renal failure, systemic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Warnings: Do not administer full strength. KAON-CL 20% will cause gastrointestinal irritation if administered undiluted.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: Nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effect is hyperkalemia (see Contraindications, Warnings and Overdosage).

Overdosage: If excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes. Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

How Supplied: Pints, gallons and 4 fl. oz.

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The new generation
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New
Lopressor™
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Adds a measure of selectivity to other beta-blocker advantages in treating hypertension

New Lopressor™ metoprolol tartrate

Decreases blood pressure with less potential for bronchospasm

Lopressor, a relatively selective beta blocker, is an effective and well-tolerated antihypertensive

Lopressor exerts a preferential effect on the beta receptors involved in lowering blood pressure and has less effect on beta receptors not involved in blood pressure control.

It concentrates its action on beta receptors in the heart (β_1) and leaves beta receptors in the lungs (β_2) relatively unblocked.

WARNING: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. However, Lopressor may be prescribed with caution for hypertensives with asthma or COPD who do not respond to, or cannot tolerate, other antihypertensive therapy. Since β_1 selectivity is not absolute and diminishes with increased dosage, a β_2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval.

Logical complement to a diuretic

The effectiveness of Lopressor combined with a diuretic was demonstrated in a study* of 15 hypertensive patients whose blood pressure was reduced on a thiazide alone, and still further reduced when metoprolol was added to the regimen. On a regimen of 100 mg hydrochlorothiazide daily, the maximal response was a mean supine blood pressure reduction of 19/10 mmHg —from a placebo-treatment baseline level of 169/115 mmHg. Following four weeks during which metoprolol 50 mg b.i.d. was added to the regimen, there was a further decrease of 17/13 mmHg.

Mild, transient side effects

Most side effects are mild and transient. The mos frequently reported adverse reactions (which

*Mitenko P, McKenzie J: Unpublished study. Data on file, Geigy Pharmaceuticals and available on request.

Usually lacks the side-effect problems of the sympathetic inhibitors

occurred in approximately ten out of 100 patients) are tiredness and dizziness. Depression and diarrhea have occurred in about five out of 100.

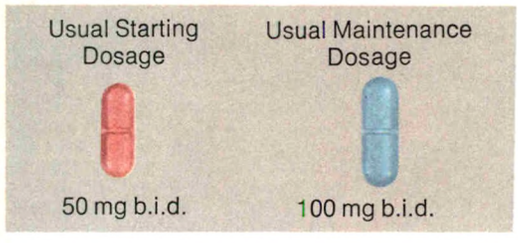
Lopressor usually lacks the side effects of the sympathetic inhibitors which may cause sedation, sexual dysfunction and postural hypotension.

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

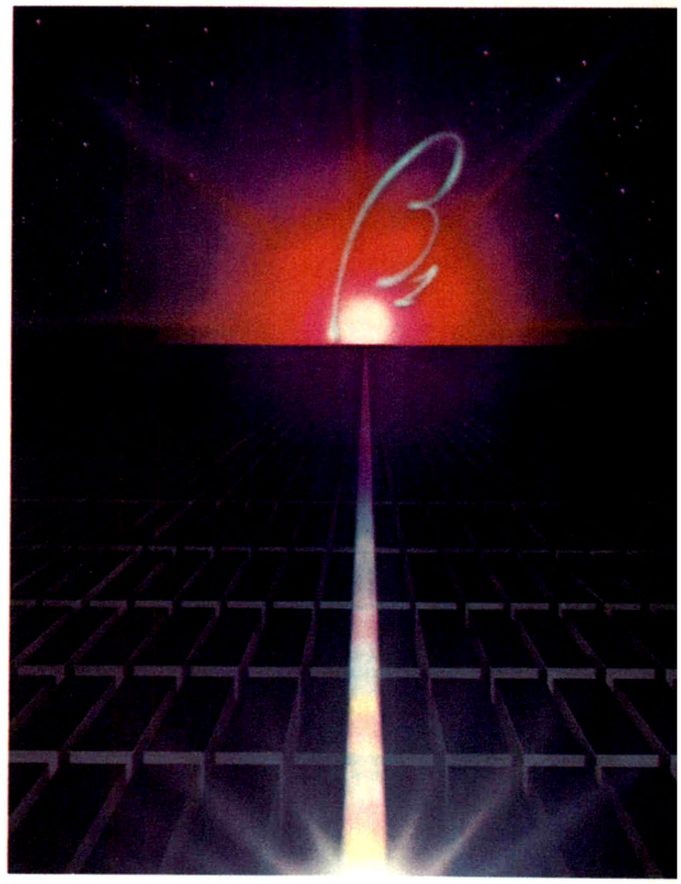
There have been reports of exacerbations of angina pectoris and, in some cases, myocardial infarction following *abrupt* cessation with other beta blockers. Even in the absence of overt angina pectoris, when discontinuing therapy, withdraw Lopressor slowly.

Simple b.i.d. dosage

Patient adherence to the regimen is likely with Lopressor because of its easy-to-remember b.i.d. dosage schedule. The usual starting dosage is one 50-mg tablet twice a day. The usual maintenance dosage is one 100-mg tablet twice a day.



While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. For further details, please see brief summary of prescribing information.



Extensive experience worldwide

Over 240,000 patients have been treated with metoprolol in 21 different countries.

Please see last page for brief summary of prescribing information.

The relatively selective beta blocker for hypertension–with simple b.i.d. dosage

Geigy

Lopressor™
brand of metoprolol tartrate

An antihypertensive beta-blocking agent

Indications Lopressor, brand of metoprolol tartrate, is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor, brand of metoprolol tartrate, is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor, brand of metoprolol tartrate, should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor, brand of metoprolol tartrate, therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor, brand of metoprolol tartrate, should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor, brand of metoprolol tartrate, may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor, brand of metoprolol tartrate, should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor, brand of metoprolol tartrate, plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor, brand of metoprolol tartrate, should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, Raynaud's disease, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor, brand of metoprolol tartrate, during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor, brand of metoprolol tartrate, should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor, brand of metoprolol tartrate, is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 1(

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Our new lithium-powered Mirel pacemaker is so compact—yet it contains all the performance features you've come to expect from Medtronic lithium pacemakers, including Constant Rate, Constant Energy, superior electromagnetic interference protection and more. And although the Mirel pacemaker is a step down in size, it's a step up in quality. This unique combination of smaller size plus a design that provides improved reliability and quality is possible due to Medtronic's exclusive advances in microcircuitry.

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The Mirel pacemaker has only 21 separate components as compared to 40 in its lithium predecessor. Benefit: less chance of component failure, fewer connections subject to failure. Mirel pacemaker components are fused by resistance welding rather than soldering. Benefit: reduced possibility of contamination.

The Mirel pacemaker uses hermetically sealed mini-paks inside hermetically sealed hybrids. Benefit: circuitry is enclosed in a redundant protected environment—an additional safety feature for your patients. And, these "mini-paks" are easily and repeatedly tested before they are connected to the hybrid substrate. Tests include centrifuge, temperature and burn-in cycles, hermeticity, shock and, of course, visual microscopic inspection.

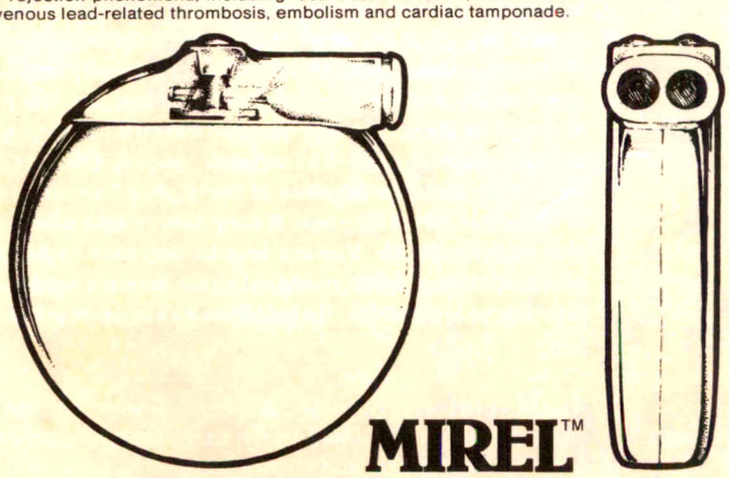
Pacing for Life™ Warranty

Another advantage, all Mirel-VL (ventricular-long-lived) pacemakers are covered by the Medtronic *Pacing for Life*™ warranty. If, during the life of your patient, the Mirel-VL pacemaker fails for any reason, Medtronic will provide a replacement product at no charge and give the same warranty on the replacement product.

There's much more to the Mirel story. Ask your Medtronic representative for details.

MEDTRONIC® IMPLANTABLE PULSE GENERATORS

Intended Uses—Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).
Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.
Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.
Precautions—The physician should be aware that all pulse generators will ultimately cease to function and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.
Side Effects—Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.



MIREL™
SHOWN ACTUAL SIZE

(Typical Physical Specifications)
Weight—60 grams • Diameter—53 mm
Thickness (center)—15 mm • Thickness (edge)—11 mm
• Available in unipolar and bipolar configuration.
Mirel™-VL has 2.2 amp hour lithium-iodine power source.
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"Variant" Angina: One Aspect of a Continuous Spectrum of Vasospastic Myocardial Ischemia

Pathogenetic Mechanisms, Estimated Incidence and Clinical and Coronary Arteriographic Findings in 138 Patients

ATTILIO MASERI, MD, FACC
SILVA SEVERI, MD
MAURIZIO DE NES
ANTONIO L'ABBATE, MD
SERGIO CHIERCHIA, MD
MARIO MARZILLI, MD
ANNA MARIA BALLESTRA, MD
OBERDAN PARODI, MD
ANDREA BIAGINI, MD
ALESSANDRO DISTANTE, MD

Pisa, Italy

From January 1970 to December 1977, transient reversible episodes of S-T segment elevation were documented in 138 patients (80 with angina only at rest, 58 with angina both on exertion and at rest). Electrocardiographic monitoring in 33 patients with hemodynamic monitoring revealed that (1) during 6,009 transient episodes of myocardial ischemia, pain was always a late phenomenon and, in some patients, often did not occur; (2) during such transient episodes, ST-T wave behavior was often variable in the same patient with alternation of elevation, depression or only T wave changes with or without pain; (3) independent of the direction of the S-T segment and T wave changes, the episodes were never preceded by an increase of the hemodynamic determinants of myocardial demand but were associated with obvious impairment of left ventricular function. Thallium scintigraphy in 32 patients revealed a regional massive and localized reduction of myocardial perfusion during S-T segment elevation and pseudonormalization of T waves. During S-T segment depression the reduction of thallium uptake was diffuse with fuzzy limits. Coronary angiography revealed no significant stenosis in 8 patients and single, double and triple vessel disease in 38, 34 and 26 patients, respectively. Angiography in all 37 patients studied during angina revealed a severe coronary vasospasm involving vessels with extremely variable extent of atherosclerosis. Severe arrhythmias were recorded in 27 patients, and a myocardial infarction occurred in 28. A total of five patients died within 1 month of hospital admission. Thus, variable intensity and extension of coronary vasospasm and the presence of collateral vessels may result in different degrees of ischemia and various electrocardiographic patterns with or without anginal pain. Vasospastic angina can occur in the presence of extremely variable degrees of coronary atherosclerosis and in any phase of ischemic heart disease. It may evolve into acute myocardial infarction and sudden death: Variant angina appears to be only its most striking electrocardiographic manifestation. When vasospastic angina is appropriately searched for, its incidence rate appears to be high.

From the C.N.R. Laboratory of Clinical Physiology and Instituto Patologia Speciale, Medica I, University of Pisa, Pisa, Italy. This study was supported in part by Subproject OD 1, Contract 77.00409.83 of the Program of Preventive Medicine, Consiglio Nazionale delle Recherche, Rome, Italy. Manuscript received March 16, 1978; revised manuscript received July 5, 1978, accepted July 7, 1978.

Address for reprints: Attilio Maseri, MD, Laboratorio di Fisiologia Clinica C.N R., Via Savi 8, 56100 Pisa, Italy.

Angina pectoris characterized by S-T segment elevation in the electrocardiogram, once considered a rare entity[1–5] and defined as a "variant" form by Prinzmetal and co-workers,[6,7] has become a frequent observation since patients with recurrent attacks of angina at rest have been routinely submitted to continuous electrocardiographic monitoring in coronary care units. Such observations have shown that this syndrome is considerably more polymorphic[8–29] than inferred by Prinzmetal et al. from their limited number of original observations. Although the role of coronary spasm in the genesis of the ischemic attacks in these patients, as previously postulated[1,5–7] appears to be "a proved hypothesis," [30] the relative incidence of "vasospastic" angina,[26,27] and its clinical and cor-

onary arteriographic characteristics are unknown as is its relation with (1) angina at rest characterized by S-T segment depression, (2) classic exertional angina, (3) myocardial infarction, and (4) sudden death.

This paper describes the characteristic features of 138 patients with "variant" angina observed in our institution during the past 7 years and the results of the diagnostic studies performed on selected groups of these patients. We will propose that the "variant" form of angina represents only one aspect of a continuous spectrum of vasospastic acute myocardial ischemia that can be observed in practically any phase of the ischemic heart disease. We will provide evidence that (1) vasospastic myocardial ischemia can occur in the presence of an extremely variable degree of coronary atherosclerosis in patients with or without a previous myocardial infarction, and with or without typical exertional angina; (2) vasospastic myocardial ischemia can also be characterized by S-T segment depression; and (3) transient vasospastic myocardial ischemia can be accompanied by chest pain or remain asymptomatic and can evolve into myocardial infarction and sudden death.

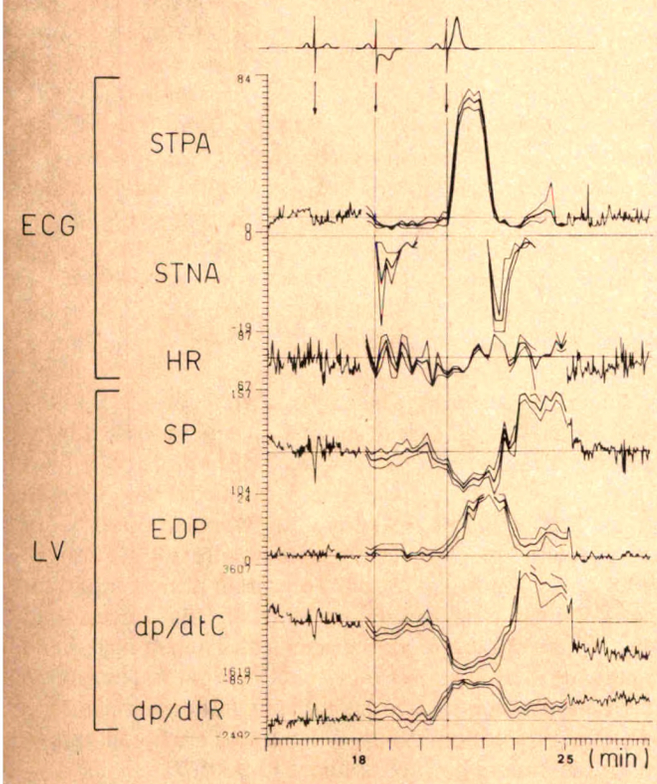


FIGURE 1. Continuous computer plot of a period of hemodynamic and electrocardiographic recording during an ischemic episode at rest. On the **abscissa** the time scale is expanded during the electrocardiographic changes (illustrated at **top**), which were asymptomatic. On the **ordinate**, electrocardiographic (ECG) and left ventricular pressure (LV) recordings are represented with the same standard error (on the ordinate). STPS and STNA = S-T segment positive and negative area, respectively; HR = heart rate; SP and EDP = systolic and end-diastolic pressure, respectively; dp/dt C and R = peak contraction and relaxation rate of rise of ventricular pressure, respectively. S-T segment changes are not preceded by hemodynamic changes indicative of increased myocardial demand. A sudden decrease in peak contraction and relaxation rate of rise of ventricular pressure precedes the onset of S-T segment elevation; a rebound of systolic pressure follows the episode (which is preceded by a brief period of S-T segment depression).

Patients

Transient reversible episodes of angina pectoris at rest characterized by elevation of the S-T segment of at least 0.2 mv not followed by permanent electrocardiographic changes or serum enzyme elevation were documented, at least once, in 129 men and 9 women aged 24 to 75 years (mean ± standard deviation 53 ± 10 years) admitted to our institution for diagnostic or therapeutic purposes, or both, from January 1970 to December 1977.

The percent of patients with demonstrable "variant" angina increased considerably in 1974 when we introduced the practice of (1) recording a 12 lead electrocardiogram *during all episodes of chest pain at rest,* before administration of nitroglycerin; (2) *submitting patients with brief episodes of chest pain to continuous electrocardiographic monitoring.*

Angina: Seventy-five men and five women (mean age 54 ± 10 years) reported a history of angina occurring either at rest or during ordinary activity but without apparent relation to the intensity of exercise and without *recognized limitation of exercise tolerance.* The angina had first occurred 2 days to 15 years before admission. Twenty-four of the 80 patients had an old documented myocardial infarction that in 9 was the first clinical manifestation of ischemic heart disease.

An additional 54 men and 4 women (mean age 52 ± 8 years) reported a history of exertional angina *with a recognized limitation of exercise tolerance.* In 32 of them exertional angina, dating from 1 to 25 years before admission, was clearly followed by the appearance of angina at rest; 11 of these had an old documented myocardial infarction. In 13, the onset of angina on effort and at rest was practically simultaneous, dating from 1 month to 10 years before admission; three of these patients had an old documented infarction. In seven patients, the onset of effort angina was preceded for a variable period (6 months to 11 years) by angina only at rest; one of these seven had an old documented myocardial infarction. In six patients, exertional angina appeared after a myocardial infarction (1 to 13 years before admission).

We observed a wide overlap among patients with a history of angina only at rest and those who reported a fixed limitation of exercise tolerance with the exception of a slight, but not significant, increase in incidence of risk factors, severity of atherosclerotic lesions and coexisting episodes of S-T segment depression during angina at rest. We therefore grouped all patients together for subsequent analysis.

In 88 patients the anginal attacks had become more frequent, more severe and of longer duration, with the characteristics of "crescendo" angina,[31,32] in the preceding 1 to 4 weeks. Fourteen patients reported a history of fainting; in 10 others, episodes of ventricular fibrillation, ventricular tachycardia or complete atrioventricular (A-V) block were documented in other hospitals.

Risk factors: The incidence of risk factors commonly associated with ischemic heart disease was the following: Thirty percent reported a familial incidence (in one of the parents, brothers or sisters), 27 percent had clinically documented diabetes, 17 percent had blood cholesterol values higher than 250 mg/100 ml, 50 percent had blood triglyceride values higher than 150 mg/100 ml, 17 percent had stable diastolic blood pressure greater than 95 mm Hg and 92 percent were smokers.

Other clinical factors: Two patients had mild rheumatic aortic regurgitation, 19 had chronic obstructive or restrictive lung disease and 6 had mild chronic renal disease. The remaining patients had no recognized associated symptomatic disease. No patient had congestive heart failure, but a third or a fourth heart sound was heard consistently or occasionally in 72 percent of patients The electrocardiogram at rest was normal in 44 patients but showed unequivocal signs of myocardial infarction in 45. The chest X-ray film showed mild to moderate cardiac enlargement in 29 patients and signs of interstitial fluid accumulation in 7.

Readmissions: Forty-nine patients were readmitted one or more times because of recurrence of angina at rest. During readmissions S-T segment elevation was documented in different leads to three patients; S-T segment depression rather than elevation in the same leads in four and S-T segment depression in other leads in two. The remaining patients continued to show S-T segment elevation at the usual sites during the attacks.

Medical management: Patients with "crescendo" angina and patients with anginal episodes of short duration were admitted or transferred to the intensive or

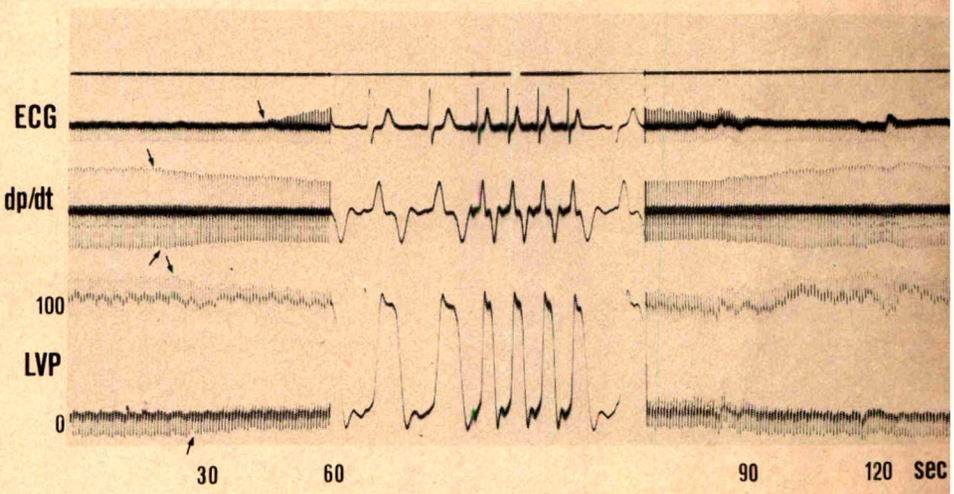


FIGURE 2. Analog playback of one asymptomatic episode of T wave change in the electrocardiogram (ECG) (lead V_4). Note the reduction of left ventricular peak rate of rise of pressure (dp/dt) and systolic pressure and the increase of diastolic pressure in the left ventricular tracing (LVP), preceding the onset of T wave changes (onset of changes indicated by **arrows**).

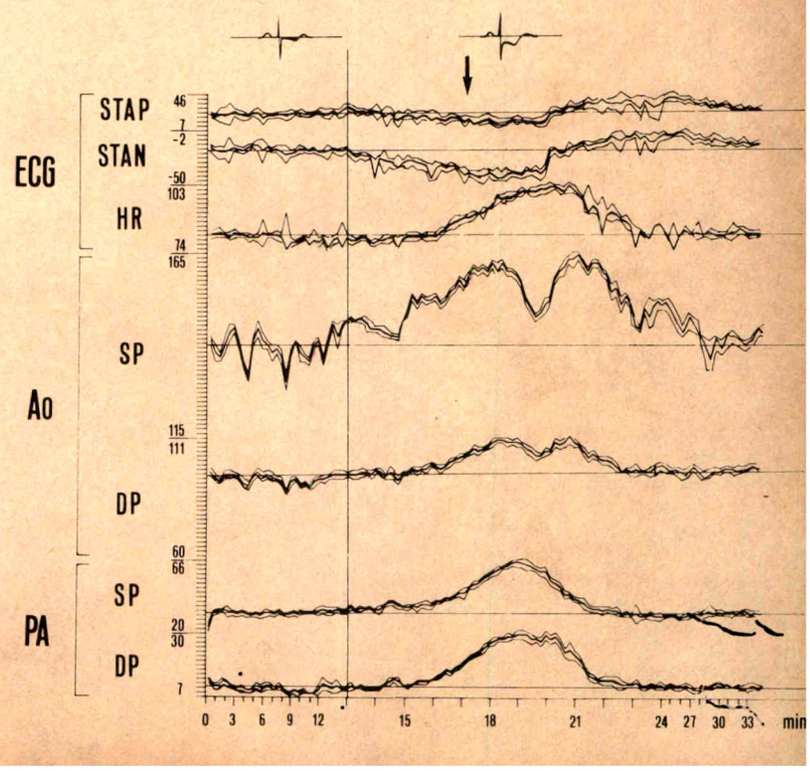


FIGURE 3. Same patient as in Figure 1. Continuous computer plot in a patient who had only angina with S-T segments depression during his second admission. Same representation as Figure 1 except for Ao and PA, which represent aortic and pulmonary pressure, respectively. No significant changes in pressure or heart rate precede the onset of S-T segment depression (lead V_5); the 6 mm change in systolic pressure (SP) at the onset of S-T segment depression is within the range of the oscillations observed during the control period. Pain begins at **arrow**: at this time systolic aortic pressure (SP) is increased by 20 mm Hg and heart rate is increased by 6 beats.

subintensive coronary care unit for variable periods; the remaining patients were hospitalized in the adjacent wards. They underwent diagnostic studies after giving informed consent and received medical treatment as required by their clinical condition. The medications used varied over the years: During the first 4 years, patients were primarily treated with orally administered nitrates and with large doses of propranolol (usually more than 200 mg/day) and practolol; in recent years, they were treated with large doses of nitrates (intravenous,[33,34] sublingual and oral) and with verapamil, a calcium antagonist drug.[35,36] Benzodiazepines (usually diazepam, 4 to 15 mg/day) were administered to reduce anxiety.

Special Investigations

Continuous Electrocardiographic Monitoring

Patients were submitted to continuous electrocardiographic monitoring in our intensive or subintensive coronary care unit for periods of 2 to 196 days (mean 27 ± 24 days) (the longer periods refer to patients who had multiple admissions). The lead showing the most marked S-T segment changes was monitored. Complete 12 lead tracings were recorded during the course of anginal episodes whenever possible. Only nine patients were not monitored; in these, transient reversible S-T segment elevation was documented with 12 lead tracings in the ward during at least one episode of angina at rest.

The most striking observations made possible by the long duration of electrocardiographic monitoring was the documentation of a large number of ischemic episodes that, in any given patient, often varied widely in (1) duration (sometimes from 30 seconds to 20 minutes); (2) electrocardiographic pattern (number of leads involved, sequence of T wave and S-T segment changes and the direction and magnitude of these changes); and (3) the presence or absence of chest pain during typical S-T segment changes.

Presence or absence of chest pain: A total of 6,009 spontaneous episodes of transient reversible electrocardiographic S-T segment changes characterized by elevation or depression greater than 0.2 mv in at least one lead were documented. Pain was present only in 32 percent of the episodes (28 percent characterized by S-T segment elevation and 4 percent by depression); it was absent in 68 percent of the episodes (61 percent characterized by S-T segment elevation and 7 percent by S-T segment depression). When present, pain occurred from 30 seconds to several minutes after the onset of the electrocardiographic changes. The asymptomatic episodes were indistinguishable from those accompanied by typical chest pain except for their usually shorter duration (from 30 seconds to 6 minutes compared with 2 to 20 minutes for episodes with pain).

Frequency of ischemic episodes: The frequency of the ischemic episodes (calculated as the average number of episodes in 3 consecutive days of monitoring during the most acute phase of the disease) was less than 1 episode/week in 13 patients, more than 1 episode/week in 36, more than 1 episode/day in 76 and more than 10 episodes/day in 13. The elevation of the S-T segment (often accompanied by variable degrees of reciprocal or nonreciprocal S-T segment depression in other leads) occurred in anterior leads in 95 patients and in inferior leads in 43.

Electrocardiographic changes: Episodes of S-T segment elevation in other leads (inferior rather than anterior or vice versa) were occasionally observed in 7 percent of patients. Often the episodes of S-T segment elevation were followed by T wave inversion or by S-T segment depression with positive or negative T waves, lasting from a few seconds to several minutes. On other occasions, transient reversible episodes of S-T segment depression were observed as the only manifestation of the ischemic episode. They occurred in the same leads usually showing S-T segment elevation in 13 percent of the patients and in different leads (not reciprocal of S-T segment elevation in opposite leads) in 5 percent of the patients. Patients with negative T waves in the control tracing usually showed pseudonormalization of previously inverted T waves 10 to 30 seconds before frank S-T segment elevation. Sometimes transient pseudonormalization of previously inverted T waves was the only electrocardiographic change during angina (see Fig. 5B and next paragraphs). On other occasions, obvious transient changes in the polarity of T waves were observed in the absence of anginal pain: These episodes were not included in the total number.

Continuous Hemodynamic Monitoring

To establish whether the anginal attacks at rest were caused by an increase in values of the hemodynamic variables known to affect myocardial oxygen consumption, we monitored right and left ventricular pressures or pulmonary arterial and aortic pressures, or a combination of these, in 22 patients with very frequent anginal attacks, using a technique previously described.[18,37,38] One patient was studied during readmission when he showed only episodes of angina at rest characterized by S-T segment depression in anterior leads, rather than S-T segment elevation documented during a previous admission. These studies were performed predominantly during the night; the tracings were recorded on an analog tape recorder (Philips Analog 14) for 10 to 24 hour periods and analyzed manually after playback on a photographic recorder and with a computer program after digital conversion.[18,37,38]

Two patients had no ischemic episodes during the monitoring period; in the others we recorded 153 episodes of S-T segment elevation, 92 of which were asymptomatic and 50 episodes of S-T segment depression, 35 of which were asymptomatic. We also recorded episodes characterized only by an increase in voltage of the T waves, with a pointed aspect, or by transient pseudonormalization of previously negative T waves (21 with typical pain and 114 asymptomatic).

Typical hemodynamic pattern: No consistent increases in heart rate, blood pressure or first derivative of left ventricular pressure (dP/dt) were observed in any patient before the onset of S-T segment elevation or depression or T wave changes (Fig. 1 to 3). *The most*

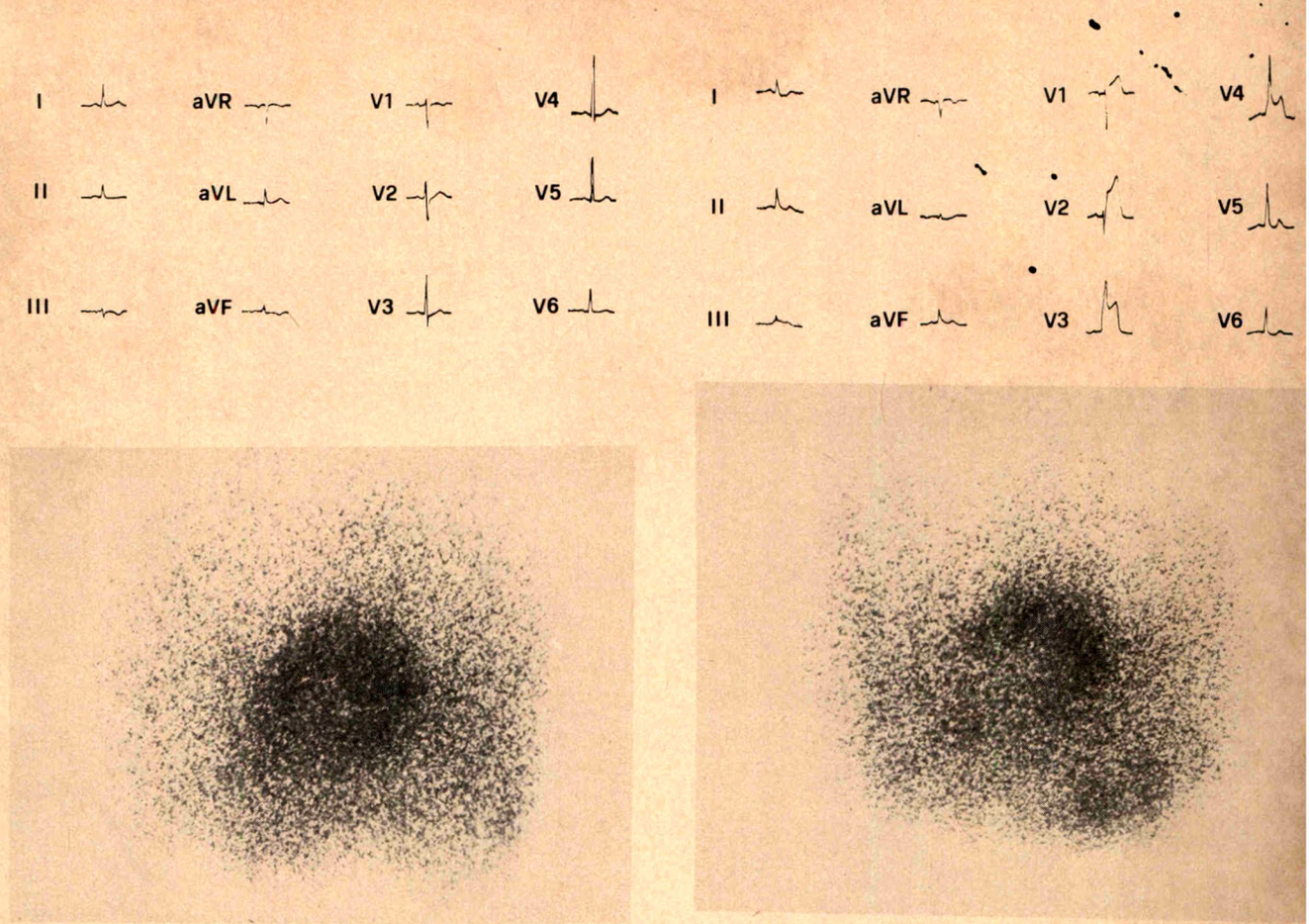


FIGURE 4. Myocardial thallium scintigrams in 45° left anterior oblique projection with corresponding 12 lead electrocardiogram obtained in the absenc of symptoms (**left**) and during an anginal episode induced by ergonovine (**right**). Coronary arteriography performed during a similar episode showe an occlusive spasm of the mid portion of the left anterior descending and circumflex arteries. The elevation of the S-T segment in the anterior a inferior leads is associated with a massive deficit of tracer uptake in the inferior and anterior heart walls.

typical hemodynamic pattern observed in the initial phase of 61 episodes of S-T segment elevation with pain *was a reduction of relaxation and contraction peak dP/dt of the left ventricle.* This change slightly preceded or accompanied the onset of S-T segment and T wave elevation and was immediately followed by an increase in end-diastolic pressure in 27 episodes. During some episodes, values for end-diastolic pressure of up to 40 mm Hg were recorded. An early decrease in systolic pressure was also observed in 27 episodes (Fig. 1). Pulmonary arterial pressure decreased after the onset of S-T segment elevation in all 16 episodes studied. Similar patterns were also observed in 87 of 92 asymptomatic episodes characterized by S-T segment elevation and in 36 episodes characterized by S-T depression (symptomatic or asymptomatic) (Fig. 1). A similar pattern was also observed in 94 episodes characterized only by transient pseudonormalization of negative T waves or by an increase in T wave voltage.

An increase in heart rate and blood pressure was often observed some minutes after the onset of the S-T segment changes, particularly in symptomatic episodes (Fig. 1 to 3). In four patients episodes of S-T segment elevation and depression alternating in the same lead were observed (Fig. 1).

Regional Myocardial Perfusion Studies

Regional myocardial perfusion during anginal attack was investigated in 32 patients with thallium-20 imaging according to the technique previously de scribed.[24,39] The study was performed during an episod of S-T segment elevation in 26 patients and during a anginal episode characterized only by pseudonormal zation of previously inverted T waves in 4. Two patient were studied twice, once during an episode of S-T seg ment elevation and once during an episode of S-T seg ment depression. The attacks occurred spontaneousl in 17 instances and were induced by intravenous injec tion of ergonovine maleate[40,41] in 15. We injected a tes dose of 0.05 mg; when ineffective, additional doses of u to a total of 0.2 mg and (more recently) up to 0.5 m were administered.

Scintigraphic findings during ischemic episod In 25 of 26 patients in whom thallium-201 could be in jected during the course of an ischemic episode with S- segment elevation, myocardial scintigraphy revealed massive transmural deficit of tracer uptake corre sponding to the electrocardiographic leads involve (Fig. 4). In the patient with a negative scan, the attac subsided about 1 minute after the injection, and scin tigraphy was performed 10 minutes later.

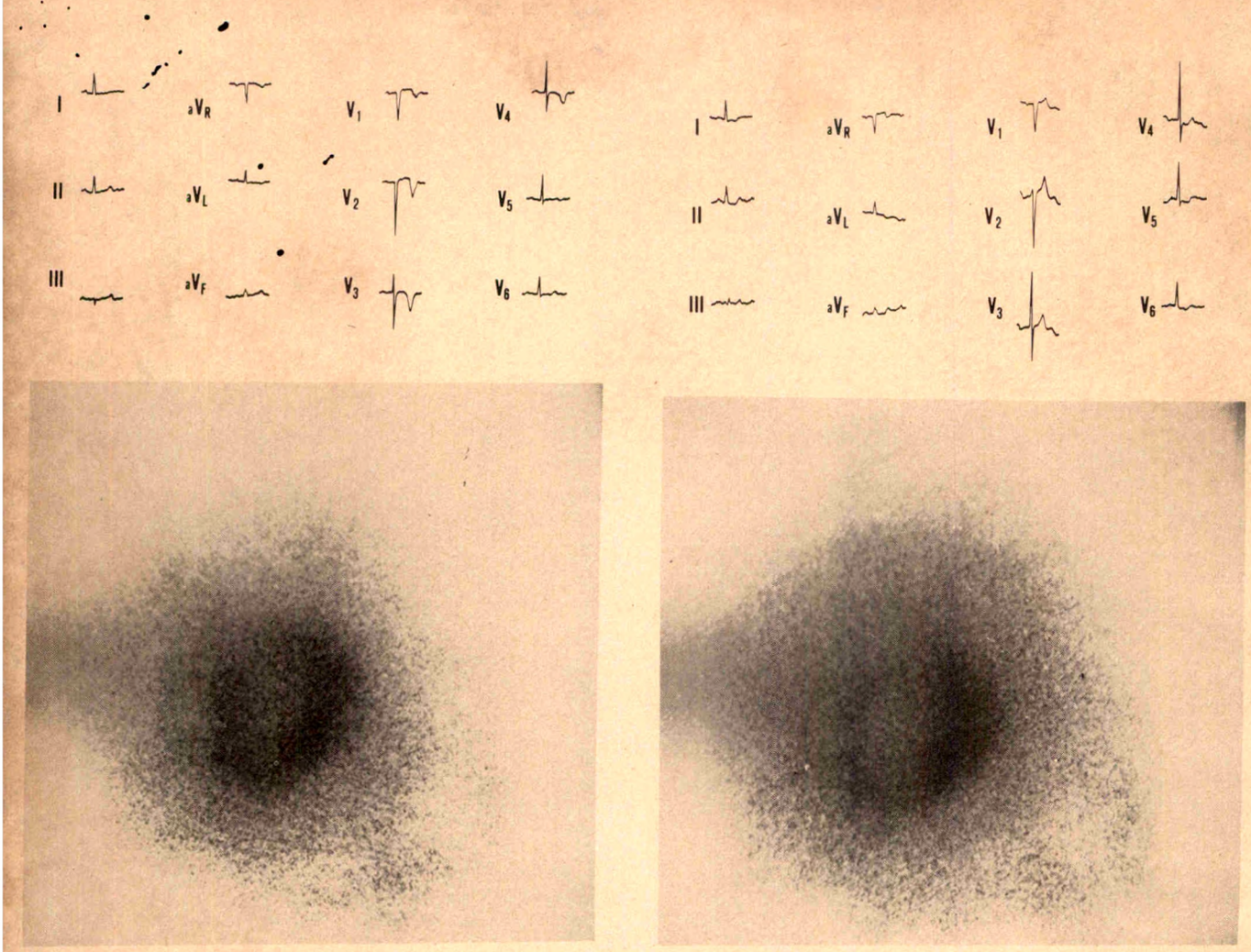


FIGURE 5. Myocardial thallium scintigrams with corresponding electrocardiogram obtained in the absence of symptoms (**panel A**) and during a spontaneous anginal episode (**panel B**). Coronary arteriography performed during a similar episode revealed a severe diffuse narrowing with delayed filling and runoff of the left anterior descending artery. There is localized old anterior myocardial infarction (**left**). Pseudonormalization of the T wave is associated with a severe anterior and septal reduction of tracer uptake in the scintigram (**right**).

The four patients studied during transient pseudonormalization of T waves also showed massive transmural tracer deficits (Fig. 5). The two patients who could be studied during an episode of S-T segment depression also showed a severe reduction of regional myocardial thallium uptake relative to control conditions, although the deficit was less massive than in episodes of S-T segment elevation and had more fuzzy limits (Fig. 6).

Angiographic Studies

Coronary arteriography and ventriculography were performed using the Judkins technique[42] in 107 patients. The study was not performed in the 10 patients older than 65 years, the 12 patients with a recent myocardial infarction or the 9 who did not consent to the procedure. In 37 patients repeated coronary dye injections could be performed during the course of an anginal episode that occurred spontaneously in 12 and was induced by ergonovine maleate in 20. In five patients angiograms could be obtained both during a spontaneous and an induced attack.

Findings in control conditions: The coronary arteriograms performed in the absence of symptoms or electrocardiographic signs of acute myocardial ischemia, or both, revealed no significant coronary stenosis in 9 patients and single, double, and triple vessel disease (50 percent or more reduction in diameter), respectively, in 38, 34 and 26 patients. Of the patients with a history of fixed limitation of exercise tolerance only 1 had a normal angiogram, whereas 15, 13 and 19 had, respectively, single, double and triple vessel disease.

Findings during acute transient myocardial ischemia: Contrast injections performed during episodes of transient myocardial ischemia, indicated by typical chest pain or S-T segment elevation, or both, showed severe reversible coronary vasospasm in all 37 patients. The appearance of the spasm was variable in different phases of the ischemic episode. Although complete occlusion with no distal filling was the most

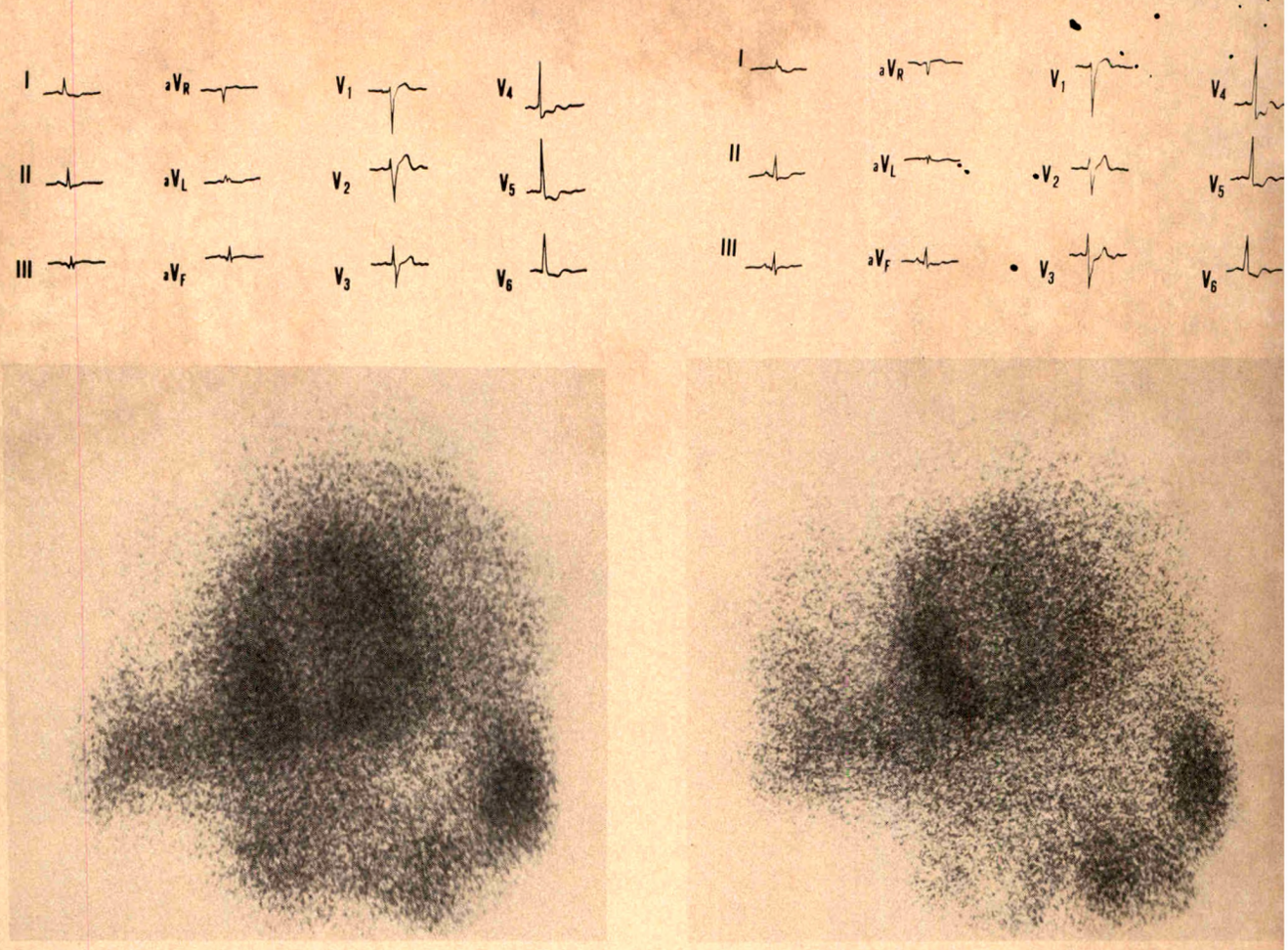


FIGURE 6. Myocardial thallium scintigrams with corresponding electrocardiogram in the absence of symptoms (**left**) and during a spontaneou anginal attack characterized only by S-T segment depression (**right**). Coronary arteriography performed during a similar episode revealed sever diffuse narrowing of a large obtuse marginal branch with poor delayed filling and with luminal reduction of the diagonal branches (the patient ha severe triple vessel disease with intra- and intercoronary collateral vessels). Increased depression of the S-T segment in lead V_5 is associate with diffuse reduction of tracer uptake at the base and in the lateral wall of the heart.

usual finding (see next paragraph), spasm diffusely involving a main vessel and its branches, with delayed filling and runoff but without complete occlusion, was observed at the beginning and during the waning phase of the ischemic episodes (Fig. 7). Similar appearances were also observed during episodes of S-T segment elevation or during episodes characterized only by transient pseudonormalization of T waves. Occlusive spasm with poor distal filling of the left anterior descending and circumflex vessles was observed in a patient with S-T segment elevation in both the inferior and anterior leads (the thallium study of this patient is illustrated in Figure 4). Spasm of a septal branch (Fig. 8) and of a diagonal branch (Fig. 9) was observed in two patients during an episode characterized by S-T segment depression, respectively, in leads V_2 to V_5 and V_3 to V_5. During a previous admission, one of these patients had angina at rest with S-T segment elevation in inferior leads and a documented spasm of the right coronary artery (Fig. 8).

Spontaneous versus provoked ischemic attack

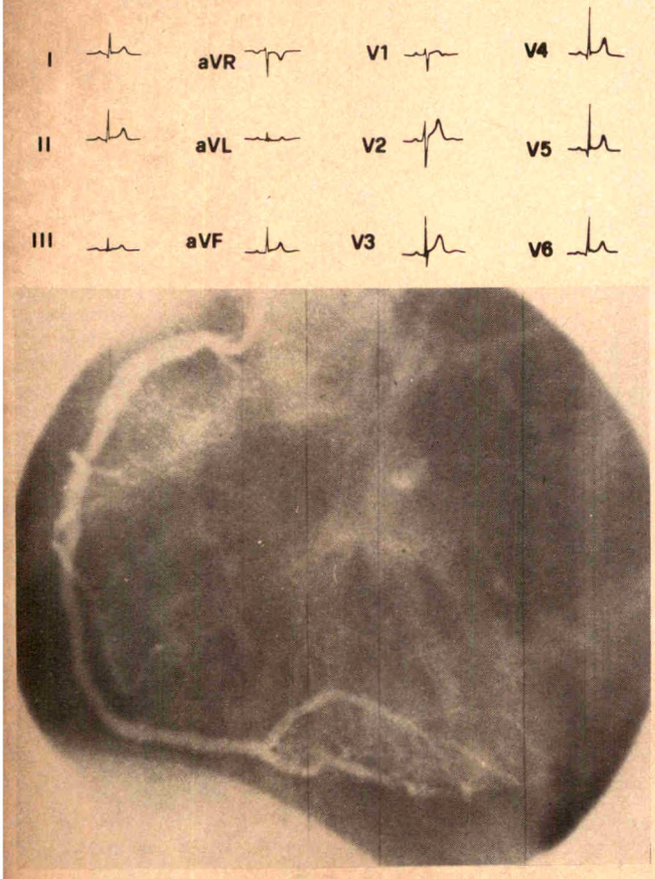
In the five patients who underwent angiography durin both spontaneous and ergonovine-induced episodes, w were unable to identify consistent differences in th appearance of spasm. In two patients complete vess occlusion was observed during a spontaneous attack an diffuse luminal reduction during an attack induced b ergonovine; in another patient the reverse was observe These differences may be related to the intensity of th vasospastic stimulus as well as to the phase of the attac in which angiography was performed. In eight patien a transient stenosis or an increase in the severity of stenosis was observed in the absence of symptoms or acute electrocardiographic changes; such changes we noted during one or more injections (whereas they we absent in others) in vessels that during the anginal a tack became completely occluded by vasospasm.

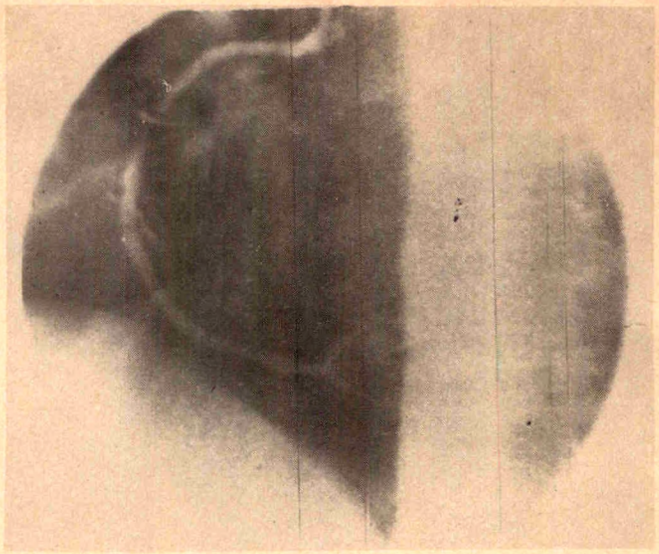
Relation of vasospasm to atherosclerotic lesion

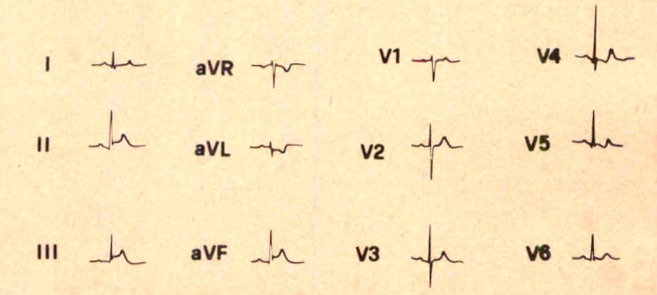
The severity of vasospasm during the central phase the ischemic episode and its location relative to th

degree of coronary atherosclerotic obstructions is illustrated in Table I. It involved normal or slightly irregular vessels with complete occlusion and no distal filling in two patients, with faint distal filling in one patient and with diffuse narrowing and delayed filling and runoff in one patient. It involved the stenotic vessel in 12 patients with single vessel disease with no distal filling in 6, with some poor distal filling in 3 and with diffuse narrowing and delayed filling and runoff in 3.

The majority of coronary spasms were documented in patients with double or triple vessel disease, who represented nearly 60 percent of our population. The artery involved by the spasm was not consistently less or more severely involved by the atherosclerotic process







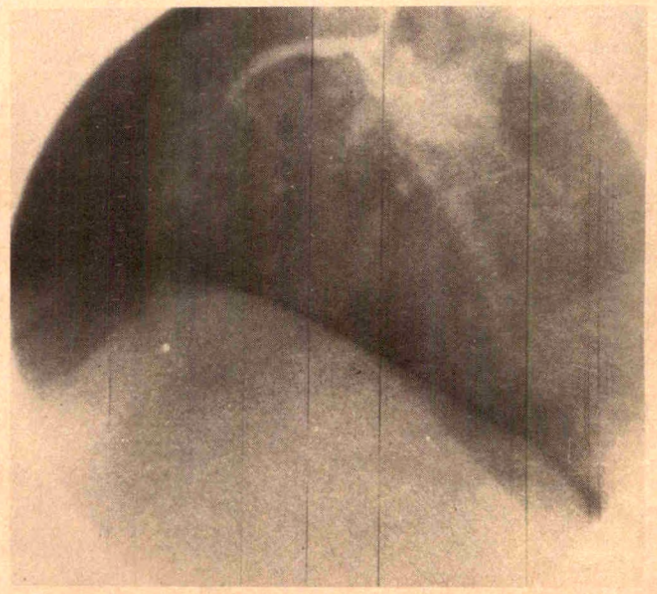


FIGURE 7. Right coronary angiograms with corresponding electrocardiogram during absence of symptoms (**above**), and at the very beginning of a spontaneous S-T segment elevation in lead III (**upper right**) and during angina (**lower right**). Diffuse narrowing at the middle third of the vessel with delayed filling and washout precedes complete proximal occlusion in the **panels at right.** No electrocardiogram is available for the **panel at upper right,** which was taken fortuitously at the onset of the attack.

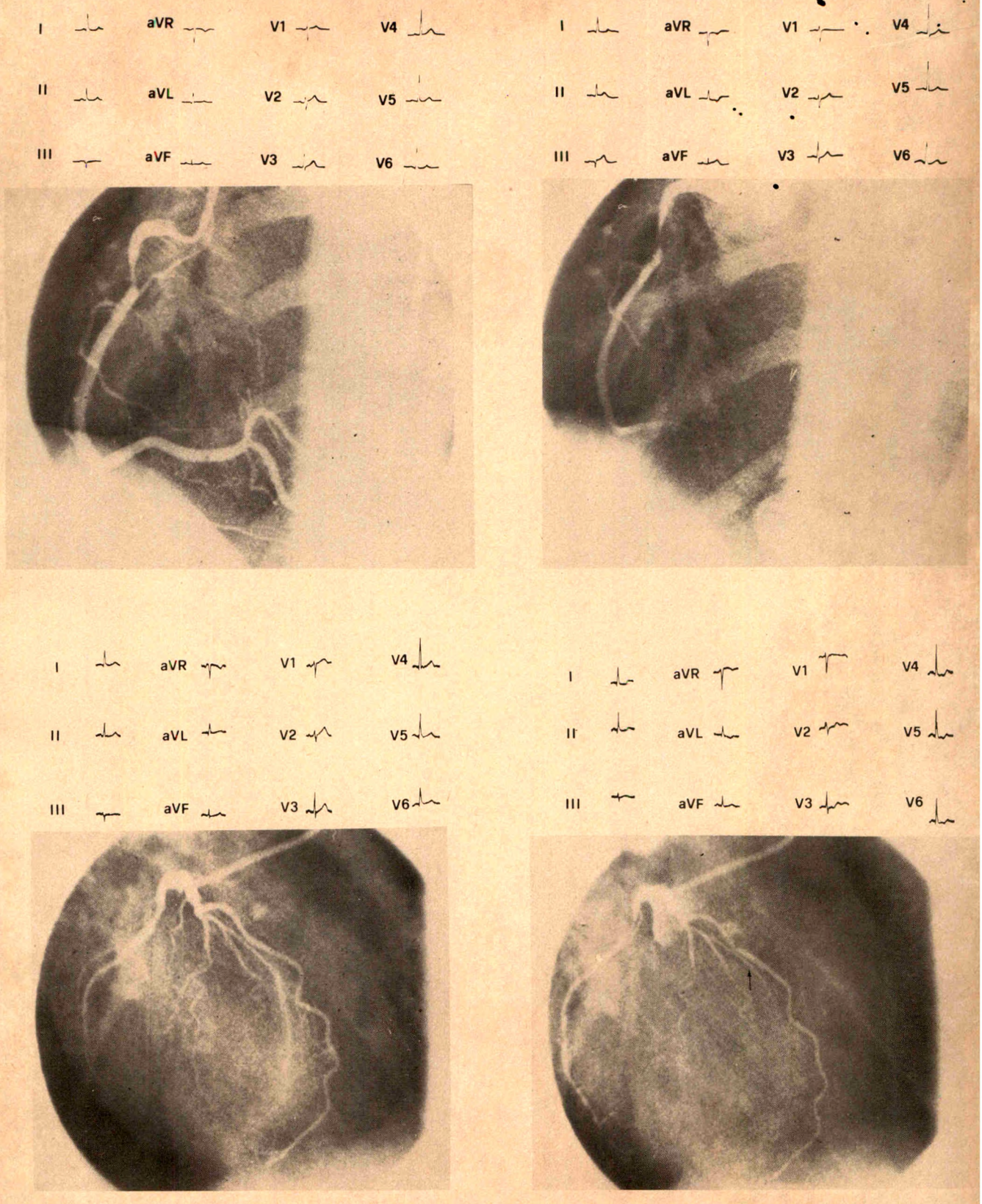


FIGURE 8. Right (**upper left and upper right**) and left (**lower left and lower right**) coronary angiograms with corresponding electrocardiogram performed in the same patient during two successive admissions. During the first he had angina with S-T segment elevation in inferior leads associated with diffuse spasm of the right coronary artery (**upper right**); during the second admission he had angina with S-T segment depression in $V_2 - V_6$. Compared with the control angiogram (**lower left**), during the second spontaneous attack (**lower right**) there was diffuse constriction of the left coronary branches with severe narrowing and delayed filling of the first septal branch (**arrow**).

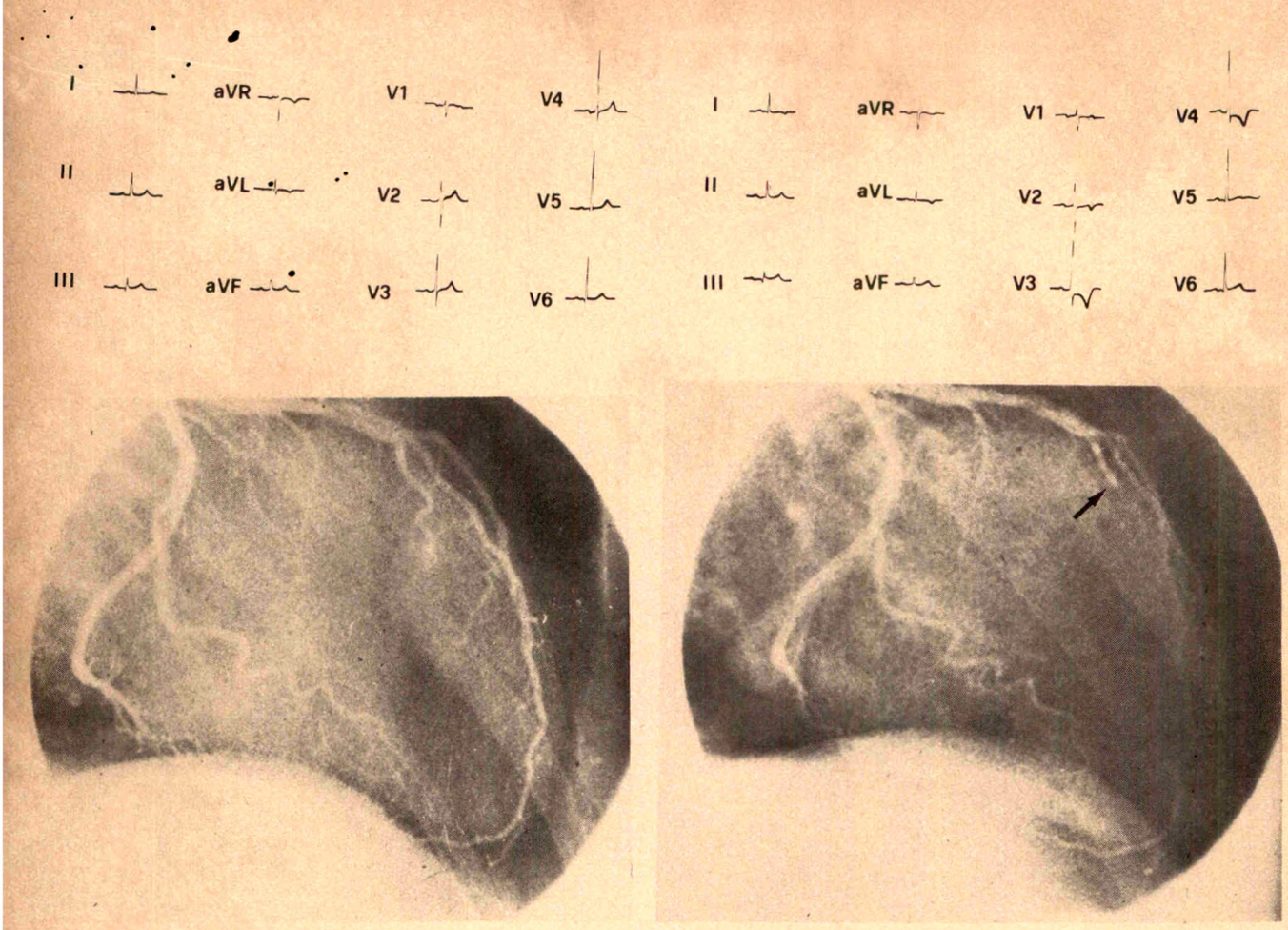


FIGURE 9. Left coronary angiogram with corresponding electrocardiogram performed in the absence of symptoms (**left**) and during angina (**right**). The patient usually had S-T segment elevation in leads V_2 to V_5. During this spontaneous episode S-T segment depression is associated with complete transient occlusion of a diagonal branch of the left circumflex artery (**arrow**) and with narrowing of adjacent branches.

TABLE 1

Severity of Spontaneous or Ergonovine-Induced Coronary Vasospasm in Relation to Extent of Coronary Artery Disease

	Normal Vessels			1 Vessel Disease			2 Vessel Disease			3 Vessel Disease		
	LAD	LCx	RCA	LAD	LCx	RCA	LAD	LCx	RCA	LAD	LCx	RCA
Occlusion without distal filling	S	...	S-E*	S-E†	E	...	S	...	...	E	E	S
				E			S-E*					
				E			S					
				S-E			S					
				E								
Occlusion with poor distal filling	...	...	S	E	...	S	...	...	S‡	E§	E§	S
						S	E			S		
							E					
							S					
Diffuse lumen reduction, delayed filling	...	...	S-E	E	...	...	E	...	...	E	...	...
				E			S			E	...	...
				E			E			S	...	...
							E					

* Spasm not occlusive after ergonovine maleate.
† Spasm occlusive only after ergonovine maleate.
‡ Spontaneous spasm in right coronary artery; in a second study, 3 months later, spasm of first septal branch (see Fig. 9).
§ Simultaneous spasm of left anterior descending and right coronary arteries.
E = ergonovine-induced attack; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; S = spontaneous attack; S-E = spontaneous and ergonovine-induced attacks.

than the other arteries. The spasm was occlusive with no distal filling in seven patients, with some faint distal filling in seven patients and with diffuse narrowing and delayed filling and runoff in seven patients. Under control conditions intercoronary collateral vessels were visible in five patients, and intracoronary collateral vessels were visible in four others. No changes in preexisting collateral circulation were observed during anginal episodes. By contrast, during an ischemic episode faint retrograde intracoronary collateral filling, distal to a transiently occluded main branch, appeared in two patients and intercoronary collateral filling could be detected in one patient in whom the controlateral vessel was selectively injected during the ischemic episode.

Electrocardiographic Stress Test

A sitting bicycle stress test was performed in 96 patients. It was not performed in patients with a recent myocardial infarction or with very frequent or prolonged anginal attacks or with a history of angina occurring consistently at minimal levels of effort. The test was multistage with continuous three lead electrocardiographic monitoring and with cuff manometer measurements of arterial blood pressure every minute. The test was conducted on end point of 90 percent of predicted maximal heart rate, fatigue or occurrence of diagnostic S-T segment changes, angina, rhythm disturbances or marked changes of arterial pressure.

S-T changes: The minimal work load reached by the patients was up to 50 watts/min. No diagnostic changes were observed in 29 patients (11 of 41 with and 18 of 55 without a history of fixed exercise limitation). Significant S-T segment depression (greater than 1.5 mm of horizontal or downsloping depression) was observed in the same electrocardiographic leads that showed S-T segment elevation during angina at rest in nine patients, S-T segment depression in the same leads and also in other leads was observed in two patients and significant S-T segment depression only in other leads (anterior instead of inferior leads or leads V_4 to V_6 instead of V_1 to V_3) was observed in 13 patients. Elevation of the S-T segment in the same leads involved during the spontaneous attacks at rest was observed during the effort test or in the immediate recovery phase in 16 patients. During the effort test one patient showed S-T segment elevation in inferior leads whereas he always had S-T segment elevation in the anterior leads during angina at rest. Transient pseudonormalization of deep negative T waves with typical chest pain was observed during or after the test in 16 patients.

Hospital Course

The hospital course of the patients with "crescendo" angina was usually more difficult than that of other patients; however, it was not unusual for these patients to become nearly asymptomatic after admission or for patients with few weekly episodes to experience worsening symptoms during hospitalization.

Fatal outcome: Five patients died during hospitalization. Two patients had intractable electromechanical dissociation during a severe anginal episode; a third patient, with good remission of angina and about to be discharged, was found unconscious in a toilet with coarse irreversible ventricular fibrillation. All three had severe triple vessel disease and old myocardial infarction, confirmed at postmortem examination in two cases. Two patients died after an acute myocardial infarction developed, one 6 hours later with intractable cardiogenic shock and the other 2 weeks later because of massive mitral regurgitation. One had triple and one had double vessel coronary disease. No other patient died up to 1 month after admission as documented by the follow-up of the patients discharged before that time.

Myocardial infarction: Acute myocardial infarction occurred in 28 patients. It was documented by persisting S-T changes, development of abnormal Q waves and with the exception of a patient who died 6 hours after the onset of symptoms, elevation of serum enzyme values. The infarction occurred 1 to 20 days after admission; it was anterior in 16 patients and inferior in 12.

In all patients the infarction developed in the heart wall corresponding to the location of the electrocardiographic changes during the anginal attacks. In four of these patients, previous hemodynamic monitoring studies had shown that the anginal episodes were not caused by increased myocardial metabolic demands; in seven, thallium-201 imaging studies during angina attacks had shown a regional transmural massive reduction of regional perfusion; in six, coronary arteriography during anginal attacks had shown vasospasm of the corresponding arterial branch. In 9 of 10 patients who underwent coronary arteriography, a critical coronary atherosclerotic stenosis of the branch corresponding to the heart wall involved by the infarction had been observed. A 24 year old woman who manifested an anterior infarction had a normal left anterior descending coronary in which occlusive spasm was observed during a spontaneous attack of angina 2 weeks before the infarction. She was not using oral contraceptive agents.

After the development of myocardial infarction anginal attacks disappeared in 1 patient, decreased in frequency in 4 patients and continued in 22, often showing normalization of the inverted T waves in the same location rather than frank S-T segment elevation. There were no other episodes of myocardial infarction up to 1 month after admission.

Arrhythmias: Ventricular tachycardia or fibrillation or complete atrioventricular (A-V) block was observed during ischemic episodes with or without pain in 21 patients (tachycardia in 19, fibrillation in 9 and A-V block in 9. Some patients had more than one type of arrhythmia). The arrhythmia had the tendency to recur in the same patient. The incidence of ectopic beats (isolated or in bursts) was common and similar in symptomatic and asymptomatic episodes; ectopic beat

recurred in some patients and were rarely seen in others. Fourteen patients underwent defibrillation or resuscitation, or both, one or more times in the coronary care unit because of episodes of severe rhythm disturbances. In two hospitalized patients with good remission of symptoms syncope developed during unheralded anginal episodes because of paroxysmal ventricular tachycardia and complete A-V block, respectively; both patients were successfully resuscitated. We were unable to identify particular characteristics that distinguished the patients who had potentially fatal arrhythmias from those who did not; of 19 who had coronary angiography, 3 had no critical stenosis, 7 had single vessel disease and 9 had double or triple vessel disease.

Coronary bypass operation: This was performed in 10 patients, after control of symptoms with medical treatment was achieved; no patient died. In three angina recurred (in spite of proved patency of the bypass graft in two).

Discharge: Our criterion for hospital discharge was absence of symptoms for at least 1 week. However, in some patients continuous monitoring occasionally revealed asymptomatic electrocardiographic ischemic episodes. A report on the long-term follow-up of these patients is in preparation (Severi et al., manuscript in preparation).

Discussion

Vasospasm as a Cause of Transient Acute Myocardial Ischemia

Relation of hemodynamic changes to onset of electrocardiographic changes and of pain: The demonstration that the anginal attacks at rest with S-T segment elevation or depression are not preceded by any increase in value of the hemodynamic determinants of myocardial oxygen consumption confirms and extends previous data.[18,38,43,44] Therefore, these objective demonstrations definitively prove that the episodes of acute myocardial ischemia in these patients cannot be ascribed, as has been traditional, to a limited possibility of increase of regional myocardial flow related to fixed critical coronary arterial stenosis.

Furthermore, our study provides three additional, relevant pieces of information. First, it indicates that the direction of the S-T segment changes does not appear to correspond to different pathogenetic mechanisms of ischemia,[45] but rather to differences in the extent and distribution of the ischemia. In fact, ischemic episodes characterized by S-T segment elevation or depression or by an increase in voltage of T waves or by pseudonormalization of T waves, with or without anginal pain, may occur in the same patient within a few minutes, as previously reported[9]; they are not preceded by changes in the hemodynamic determinants of myocardial oxygen demand and show similar hemodynamic patterns. Second, our study demonstrates that the sequence of events usually observed in episodes of sudden S-T segment elevation (impairment of ventricular contraction and relaxation velocity immediately before or accompanying the electrocardiographic changes) closely resembles that obtained in the dog by sudden occlusion[46,47] and release[48] of a major coronary branch. Finally, our study shows that pain is always a late phenomenon relative to the onset of ischemia and may even be absent, in accordance with previous findings.[9,18,49–51] The discordant conclusions reached by some investigators[52–54] on the cause of anginal attacks at rest are probably related to the erroneous assumption that the appearance of pain represents the onset of myocardial ischemia.[52–56] Indeed our findings indicate that arterial pressure and heart rate may become elevated only after the onset of the ischemic episode and rise even further at the onset of pain but do not change appreciably before the onset of the electrocardiographic changes.

Regional myocardial perfusion and S-T segment changes: The massive transmural deficit of regional perfusion documented during anginal attacks characterized by S-T segment elevation in these patients extends the findings of our own studies[24,39] and isolated reports.[56,57] It strongly supports the hypothesis that an acute regional reduction of blood supply is responsible for the episodes of acute myocardial ischemia. A massive transmural reduction of regional perfusion was also observed in episodes of angina with pseudonormalization of T waves (Fig. 5), thus proving the hypothesis already developed in recent articles.[58,59] A diffuse regional reduction of perfusion was documented in episodes characterized by S-T segment depression (Fig. 6) in agreement with previous findings obtained in patients who had only episodes of S-T segment depression.[60]

Our studies do not provide an absolute indication that the reduction in perfusion does indeed precede (and thus cause) the anginal attacks, because they were performed after the onset of the ischemic attack. Nevertheless, continuous monitoring of coronary sinus oxygen saturation with a fiberoptic catheter has shown that impairment of contractility and S-T segment elevation or depression are consistently preceded by a marked decrease in blood oxygen saturation,[61] thus indicating a causal role for the reduction in regional coronary flow.

Angiographic demonstration: Vasospasm during episodes of "variant" angina was documented initially more by chance than by design[62–76] and more recently in a number of systematic studies.[17–28] Our data confirm and extend these data and indicate that vasospasm is also present in episodes characterized by pseudonormalization of negative T waves or by S-T segment depression. These observations are in agreement with those made in patients with only angina at rest with S-T segment depression.[26,27,77]

Thus the vasospastic hypothesis of Latham,[78] Osler,[79] Gallavardin,[80] Lewis,[81] Parkinson and Bedford,[1] Brow and Holman[2] and Wilson and Johnston,[5] appears now to be well substantiated by objective data. The concept of Prinzmetal et al.[6,7] of an increased smooth muscle tone surrounding a subcritical stenosis must be extended because (1) at one extreme the spasm may occur in the absence of critical or subcritical atherosclerotic obstructions, and at the other it may occur in the presence of severe triple vessel disease; (2) in the presence

of obstructions, vasospasm extends proximally or distally, or both, to the organic stenosis over a variable segment of the vessel; and (3) the spasm may restrict or occlude more than one vessel and may diffusely involve also smaller arterial branches, resulting in myocardial ischemia with S-T segment elevation or depression or with only T wave changes with or without pain.

The angiographic appearance of coronary vasospasm was found to vary in subsequent phases of the anginal attack and in different attacks. Generally when the S-T segment is markedly elevated no distal perfusion beyond a major branch is detectable; on other occasions, one may observe localized or diffuse spasm or obvious narrowing of multiple branches, or both, with filling that is poor and sometimes frankly retrograde through collateral channels. *Therefore it seems reasonable to infer that intensity and extension of vasospasm and degree of collateral perfusion may result in various degrees and different transmural distributions of myocardial ischemia.* The possible mechanisms of coronary vasospasm are still largely hypothetical[41] and are beyond the scope of this report. However, it is of interest to note that cardiac denervation and even autotransplantation do not appear effective in preventing vasospasm.[82]

Recognition and Estimated Incidence of Coronary Vasospasm

If one assumes that "variant" angina may represent, with few exceptions,[83] an acceptable, easily recognizable landmark of acute vasospastic myocardial ischemia, the frequency of observation of this syndrome appears to depend on the care with which it is looked for. In our experience, the number of patients with "variant" angina rose from about 2 percent to more than 10 percent of patients admitted for anginal pain when we began to apply systematic rules for its detection. Larger series from other institutions are also beginning to be reported.[29,84]

Variant angina may be readily detected in patients admitted to a coronary care unit if repeated complete 12 lead electrocardiograms are recorded during all attacks. In fact, frank S-T segment elevation may be evident only in some episodes, in few leads and in one phase of the ischemic episode. Recording only one lead, as is commonly the case in coronary care units, may show S-T segment depression as the reciprocal of S-T segment elevation in opposite leads or accompanying minor S-T elevation or even pseudonormalization of negative T waves in other leads.

Variant angina is unlikely to be searched for in other patients for several reasons. At one extreme is the preconceived idea, accepted by the vast majority of physicians, that angina is typically brought about by exertion or emotion and relieved by rest. Thus, when confronted with a history of episodic anginal chest pain at rest with a normal electrocardiogram at rest and on effort, the physician may dismiss the patient rather than refer him to a cardiac department. At the other extreme, some patients who can sometimes perform heavy and prolonged exercise without symptoms can on other occasions experience angina on moderate effort or at rest, or both; if they are found to have some atherosclerotic narrowing in their coronary arteries, they are often judged to have only "classic" angina. In fact, a different level of myocardial oxygen demand for the same level of work is traditionally considered the *only* factor responsible for the variable anginal threshold.

Undoubtedly the incidence of vasospastic myocardial ischemia could be significantly greater than is indicated by the demonstration of "variant" angina if one considers that (1) angina at rest with S-T segment depression and with pseudonormalization of T waves also appears to be caused by vasospasm; (2) that asymptomatic ischemic episodes are frequent, as observed in our patients and as suggested by another recent study[85]; and (3) that angina induced by cold may result from vasoconstriction.[86]

Vasospasm, Electrocardiographic Changes, Coronary Atherosclerosis and "Classic" Exertional Angina

Our findings demonstrate that elevation of the S-T segment represents the most dramatic and striking electrocardiographic change characteristic of vasospastic angina rather than its only electrocardiographic manifestation. Less spectacular changes, such as S-T segment depression and pseudonormalization of T waves, may also be caused by vasospasm, depending on its location, severity, extension, the presence of collateral vessels and the pattern of the electrocardiogram at rest. These various electrocardiographic aspects can be observed in the same patient either with or without typical anginal pain. Thus although "variant" angina can reasonably be assumed to be the most easily recognized landmark of vasospastic angina, the possibility of spasm should also be carefully considered in anginal attacks at rest characterized by other electrocardiographic changes.

"Variant" angina in patients with severe coronary atherosclerosis has previously been observed,[12,15,23,25] and the existence of two diseases was postulated: "variant angina due to spasm in patients with normal or near normal coronary arteriograms and a similar clinical and electrocardiographic syndrome occurring in the setting of coronary atherosclerosis with the role of spasm in the latter group still undefined."[87] Our findings strongly support the view that, with rare exceptions,[83] variant angina is caused by coronary vasospasm independently of the severity of coronary atherosclerosis. However, the latter may be associated with a more severe prognosis and may be responsible for the coexistence of "classic" exertional angina. Patients who also reported a history of classic exertional angina represent 42 percent of all our patients. They appear to have a somewhat more extensive coronary atherosclerotic involvement than the patients who had no history of exercise limitation. However, although the presence of severe coronary atherosclerosis seems to favor the coexistence of classic exertional angina with vasospastic angina, the relation between a history of exertional angina, response to the electrocardiographic stress test and coronary atherosclerosis does not appear straight-

forward, as already observed in patients with exertional angina.[88–90] In fact, whereas negative stress tests were observed in patients with a history of exertional angina, severe atherosclerosis and positive stress tests were observed in patients who reported only angina at rest. These inconsistencies may be related in part to the subjective interpretation of symptoms by individual patients or to the avoidance of exertion because of the presence of angina at rest.

The borderline between vasospastic and classic exertional angina may also be blurred by the possible occurrence of vasospasm during physical exertion. This hypothesis is suggested by the rather frequent observation of S-T segment elevation or of pseudonormalization of T waves during a stress test or in the immediate recovery phase observed, respectively, in 17 and 16 of our patients. The finding of S-T segment elevation during stress testing has previously been reported[91–94]; because in our patients the extent of coronary atherosclerosis was not more severe than in patients with stable angina, it is conceivable that in some patients on some occasions vasospasm may also be precipitated by physical exertion as reported in one case during pacing[55] or exercise.[95] The variable sequence of the onset of exertional angina preceding, following or accompanying that of angina at rest in a large number of patients suggests that vasospastic angina may occur in the same patient before or after the onset of classic exertional angina, in addition to coexisting with it.

Finally, as indicated in a previous report,[96] some patients may experience angina because of myocardial ischemia occurring in different regions of the myocardium and resulting from different pathogenetic mechanisms. In 13 of our patients the electrocardiographic ischemic changes, characterized by S-T segment depression observed during the stress test, occurred in different leads from those showing the S-T elevation at rest, thus suggesting that the myocardial region involved by ischemia at rest and during exercise may not be the same.

Coronary Vasospasm, Sudden Death and Myocardial Infarction

The severe rhythm disturbances observed in our patients as well as in others,[15,16,23,26,71,97] and the three episodes of death with irreversible ventricular fibrillation or with electromechanical dissociation suggest that acute myocardial ischemia caused by vasospasm may be a cause of sudden cardiac death. The frequency of this event is difficult to establish because episodes of ventricular tachycardia and ventricular fibrillation were also observed during asymptomatic episodes.

The following facts support the possibility that coronary vasospasm may be one of the initiating causes of myocardial infarction as recently postulated[98,99]: (1) the incidence of myocardial infarction; (2) the occurrence of infarction in the same area undergoing transient myocardial ischemia with demonstrated transient thallium-201 perfusion deficits; and (3) the demonstration of coronary vasospasm during anginal episodes in the artery supplying the zone where the infarction subsequently occurred. This conclusion appears reasonable considering that repetitive severe vasospasm may result in endothelial damage, plaque hemorrhage with consequent platelet aggregation and release of thromboxane A_2 and further vasoconstriction.[100] Thus, speculatively, in such circumstances as yet obscure, repeated or prolonged vasospasm, or both, may initiate a vicious circle leading to prolonged coronary arterial obstruction and possibly to parietal thrombus deposition and luminal obstruction.[41]

In all but one of our patients, myocardial infarction occurred distal to a vessel with atherosclerotic stenosis, and all deaths in our study occurred in patients with double and triple vessel disease. Thus the severity of atherosclerosis appears to be associated with a more severe prognosis with regard both to the development of infarction and to the incidence of sudden death. In fact, vasospasm may compromise collateral blood supply or impair to a greater extent heart function already jeopardized by locally reduced coronary reserve or old scars, or both. Furthermore, vasospasm may be more likely to damage the arterial wall when already severely involved by atherosclerosis. However, the presence of critical coronary stenosis does not seem to be essential for the development of myocardial infarction, a finding in agreement with pathologic observations.[101] Two of our patients had an old myocardial infarction with normal coronary arteriograms and one had an anterior myocardial infarction 2 weeks after the angiographic observation of an occlusive spasm of a normal left anterior descending coronary during a spontaneous anginal attack.

Therapeutic Implications

The demonstration that coronary vasospasm may be a frequent cause of angina at rest with S-T segment elevation with pseudonormalization of negative T waves and with S-T segment depression suggests that similar observations should be undertaken in other laboratories. We suggest that diagnostic studies (thallium-201 myocardial scintigraphy during angina at rest, continuous hemodynamic monitoring or stress tests of coronary reserve such as exercise or pacing[102,103] should be performed routinely to establish whether angina at rest is "*secondary*" to the exhaustion of the limited fixed coronary reserve by an excessive increase of demands or whether it is caused by "*primary*" sudden reduction of blood supply or by other mechanisms yet unidentified. Such pathogenetic distinction between *primary* and *secondary* causes rather than clinical descriptive classifications such as acute coronary insufficiency,[104,105] intermediate coronary syndrome,[106] coronary failure,[107] status anginosus,[108] preinfarction angina[109,110] and unstable angina[31,111] should provide the basis for a rational therapeutic approach to patients with angina at rest.

A vasospastic origin of anginal attacks could explain: (1) the large incidence of normal or minimally stenotic arteries in 10 to 15 percent of patients with these syndromes,[111,112] which was the reason for their exclusion from randomized medical versus surgical trials; (2) the lack of difference in the severity of coronary atherosclerotic lesions between patients with un-

stable and stable angina.[113,114] In turn, the possible vasospastic origin of this syndrome in patients with no significant coronary atherosclerotic stenosis should suggest the possibility that the same mechanisms may operate also in some patients who happen to have significant coronary stenosis.

As to the medical management, although favorable results have been reported with nitrates,[33,34] calcium antagonists,[35,36] and very large doses of beta receptor blockers,[115] treatment of vasospastic angina will be empirical and symptomatic until the causes of vasospasm and the possible feedback mechanisms controlling its reversibility or irreversibility are elucidated. At 1 month the overall mortality rate was 3.6 percent and the incidence rate of infarction was 21 percent in our series. Thus the overall results of our empirical medical treatment compare favorably with those reported for other series of patients with unstable angina with medical and with surgical therapy.[16,20,23,25,31,32,116–120]

Bypass coronary surgery should be performed when objectively indicated by the demonstration of a coexisting severe fixed limitation to the possible increase o coronary blood supply, preferably after medical contro of the vasospastic episodes. One must await proof tha bypass operation reduces mortality or the risk of in farction, or both.

Finally, because it appears reasonable to assume tha coronary vasospasm may be one of the mechanism implicated in the genesis of myocardial infarction an of sudden cardiac death, current research efforts towar the reduction of mortality and disability from coronar artery disease should also be focused on the pathoger etic mechanisms of coronary vasospasm.

Acknowledgment

We are indebted to the paramedical personnel of our cor onary care unit and of the hemodynamic laboratory for thei cooperation, and to H. Biagini-de Ruijter and F. Cerri for thei help in the preparation of the manuscript. We are also gratefu to Lionel H. Opie, Visiting Professor, on sabbatical fror Groote Schuur Hospital, Capetown, South Africa, for a helpfu discussion and review of our manuscript.

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The Pericardium: An Essay on Some Recent Developments

RALPH SHABETAI, MD, FACC

San Diego, California

The published work on pericardial function is reviewed briefly, emphasizing experiments designed to show whether or not the normal pericardium restrains cardiac volume. Recent work from this laboratory has shown that nitroprusside infusion in hypervolemic dogs with an intact pericardium shifts the whole of the ventricular diastolic pressure-volume or dimension curve downward (less pressure for a given volume). After pericardiectomy, nitroprusside shifts the pressure-volume or dimension relation along a single curve. These studies indicate that the pericardium exerts a restraining influence on the left ventricle and that it greatly modifies the response of the left ventricle to altered preload. Recent studies from other laboratories have demonstrated that the pericardium plays a major role in the dynamic interaction between the ventricles.

Recent hemodynamic studies have shown that cardiac tamponade in patients with intrinsically elevated left ventricular diastolic pressure causes equilibration between right (but not left) ventricular diastolic pressure and pericardial pressure. Pulsus paradoxus is not found in these patients because resistance to left ventricular filling is constant throughout the respiratory cycle. Other recent hemodynamic work includes the description of occult constrictive pericardial disease and a report that effusive-constrictive pericarditis is common in neoplastic involvement of the heart and pericardium.

The spectrum of infectious pericarditis is changing; the entity still poses difficult therapeutic questions. The proper treatment of uremic pericarditis, especially with tamponade, remains highly controversial. The relative places of increased dialysis, intrapericardial poorly absorbed corticosteroids, pericardiocentesis, pericardial window and pericardiectomy are yet to be determined.

The recent renaissance of interest in the functions of the pericardium extends to the role of the pericardium in normal cardiac physiology, the possible contributions of the pericardium to the pathophysiology of cardiac failure and the major influence of pericardial dynamics on the diastolic properties of the ventricles. One must therefore take the pericardium into consideration in studies of left ventricular diastolic compliance.

This essay is not a comprehensive review of pericardial function or disease. Rather it is a discussion of selected aspects of pericardial physiology and pathophysiology that have interested me for several years, followed by a brief account of changes, some highly controversial, that are taking place in our concepts of some kinds of pericarditis.

Functions of the Pericardium

Limiting mobility of the heart: Several functions have been ascribed to the pericardium. The double-layered membrane with its potential space filled with pericardial lymph has been thought to lubricate the surface of the heart so that it can undergo motion without friction or

From the Department of Medicine, Veterans Administration Hospital, University of California, San Diego, California. This paper was supported in part by Grant HL 12373 from the National Institutes of Health, Bethesda, Maryland and Grant MRIS 7824 (normal and abnormal pericardial function and the cardiomyopathies) from the Veterans Administration, Washington, D. C. Manuscript received August 28, 1978, accepted September 6, 1978.

Address for reprints: Ralph Shabetai, MD, Cardiology Department (111A), Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, California 92161.

damage to the epicardium.[1] A proposed extension of this concept states that the pericardium with its enclosed liquid serves to equalize gravitational forces acting on the heart.[2] As every clinician knows, the heart shifts considerably with alteration of the subject's posture, but the pericardium still limits the extent of this mobility of the heart within the thorax. In patients with congenital partial absence of the pericardium the heart is not in the midline, and it moves excessively when posture is changed.[3] This phenomenon is not observed after surgical removal of the pericardium because of the dense scar that then fixes the heart in the mediastinum. The pericardium provides a means for the important lymphatic drainage of the myocardium. Lymph forms on the surface of the epicardium,[4] collects in the pericardial space and is drained into the lymphatic system. The pericardium with its active turnover of lymph is also thought to protect the heart from infection in contiguous structures.

Limiting cardiac dimensions and preventing acute distension: The function of the pericardium most germane to this discussion is its role in limiting cardiac dimensions and preventing acute distension. Bernard[5] considered that one function of the pericardium was to restrict the cardiac volume, and his view was shared by Kuno[6] and by Gibbon and Churchill.[7] Many investigators have examined the importance of the pericardium in relation to the overall cardiac dimensions or the dimensions of specific cardiac chambers, usually the left ventricle. The pericardium is also an important determinant of the relation between the diastolic pressure and the dimensions of the left and the right ventricles.

The results of several experiments designed to test the restraining effects of the pericardium on left ventricular volume have been published. When left ventricular pressure was plotted on the ordinate and left ventricular volume or one of its component dimensions on the abscissa, the resulting curve was consistently steeper with the pericardium intact than with the pericardium opened or removed. Studies have been performed using a wide variety of models ranging from the isolated nonbeating canine left ventricle[8] and the left ventricle of anesthetized acutely instrumented dogs[9] to unanesthetized chronically instrumented animals.[10] The studies that confirmed a ventricular volume-limiting function of the pericardium were performed in experiments in which the volume of the heart or left ventricle was substantially increased by volume loading. Holt et al.[11] measured intracardiac and intrapericardial pressures in dogs when they were normovolemic, after hypervolemia had been induced by transfusion and after hypovolemia created by hemorrhage. They noted the anticipated increase in the diastolic pressures of the left and right ventricles and of right atrial pressure during acute hypervolemia and observed that pericardial pressure increased during hypervolemia. When the ventricular diastolic pressure increased from 0 to approximately 10 mm Hg an equal and parallel increase in intrapericardial pressure occurred; as a result, the ventricular transmural diastolic pressure, the true filling pressure of the ventricles, was not increased. After further transfusion, the ventricular diastolic pressure increased to more than 10 mm Hg but there was little further increase in intrapericardial pressure, suggesting that the pericardium had then reached the limit of its acute distensibility.

Pressure overload of a ventricle is an alternative means of increasing ventricular dimensions. This technique has the advantage that it can be selective for one ventricle and the relative disadvantage that dimensional changes are smaller than those obtained with volume expansion. Experiments using pressure loading techniques to demonstrate cardiac restriction by the normal pericardium have yielded conflicting results.[12,13] In pressure loading experiments, the increase in ventricular volume may be less than the reserve volume of the pericardium,[13] a phenomenon that may explain why the hemodynamic effects of the pericardium cannot consistently be demonstrated by experiments of this kind.

Contribution of Pericardium to Pathophysiology of Cardiac Failure

Role of pericardium in right heart failure in left ventricular disease: Striking edema and increased systemic venous pressure have been observed in patients with severe left ventricular disease. Although much of the right heart failure can be explained by elevation of the left ventricular diastolic pressure causing pulmonary hypertension and eventual failure of the right ventricle, right ventricular function may also be impaired in these cases by bulging of the ventricular septum into the right ventricle (Bernheim syndrome).[1] Reversed Bernheim physiology—bulging of the ventricular septum into the left ventricle with resulting left ventricular dysfunction—has been postulated to explain evidence of left ventricular failure in patients with predominantly right ventricular disease.

It has been speculated that the pericardium may oppose the effects of left ventricular dilatation on right ventricular function[15] in this manner: Dilatation of the left ventricle increases intrapericardial pressure, which thus limits right ventricular filling and thereby reduces forward flow into the lungs, perhaps preventing pulmonary edema. The pericardium thus causes reciprocal shifts of the Frank-Starling curves of the two ventricles and so balances their outputs. The Frank-Starling mechanism, and in consequence the pericardium, is considered important in normal cardiovascular responses to change in body posture, and the evidence for its role in compensated heart failure is strongly suggestive.

Role of pericardium in hemodynamic interaction between the left and right ventricles: On a beat to beat basis, considerable evidence exists for a linear relation between ventricular end-diastolic volume and the subsequent stroke volume. A major function of Starling's law in normal man is to maintain nearly equal time-averaged outputs from the right and left ventricles to keep a proper volume equilibrium between the pulmonary and systemic circulations. The pericardium, by

influencing the effects of diastolic pressure and dimensions of one ventricle on the opposite ventricle, may facilitate hemodynamic interaction between the ventricles to balance the right and left ventricular outputs.

The effects of one ventricle on the other were confirmed in several elegant animal experiments, some using isolated heart preparations and some intact animals. In these studies, right and left ventricular volumes or dimensions were estimated using direct measurement[16–18] or suitably placed opaque markers.[19] These studies showed that when either the volume or the diastolic pressure of the right ventricle is increased, changes in the shape and dimension of the left ventricle consistent with bulging of the intraventricular septum are produced. These changes in turn alter the systolic function of the left ventricle. In many of these studies, the possible contribution of the pericardium to the results was not seriously considered, and in many of them the pericardium had been opened or removed.

Role of pericardium in acute mitral regurgitation: Acute mitral valve incompetence[20] occurring after sudden rupture of the chordae tendineae is a clinical condition in which hemodynamic studies have demonstrated restriction of cardiac volume by the pericardium. When patients were studied soon after the rupture, and before sufficient time had elapsed for left atrial and left ventricular dilatation, the hemodynamic findings included the sharp narrow systolic peak of left atrial pressure that approached the level of left ventricular systolic pressure, and findings in diastole that were strongly suggestive of pericardial disease, which was in fact absent. During diastole, the left atrial, left ventricular and right ventricular pressures were equal and their configuration suggested constrictive pericarditis. When patients were studied later after the chordal rupture, the findings simulating pericardial disease were no longer present. It was postulated that massive acute dilatation of the left ventricle and left atrium was prevented by the noncompliant pericardium, which limited their dilatation to the reserve volume of the pericardium. It was further hypothesized that in the more chronic cases the pericardium gradually stretched, allowing cardiac dilatation with consequent disappearance of the hemodynamic pattern that simulated pericardial disease.

Role of Pericardium in Diastolic Properties of the Ventricles

Relation between ventricular and intrapericardial pressures: Most hemodynamic studies of the pericardium have focused on diastole, but in their work Holt et al.[11] examined the instantaneous relation between ventricular pressure and intrapericardial pressure

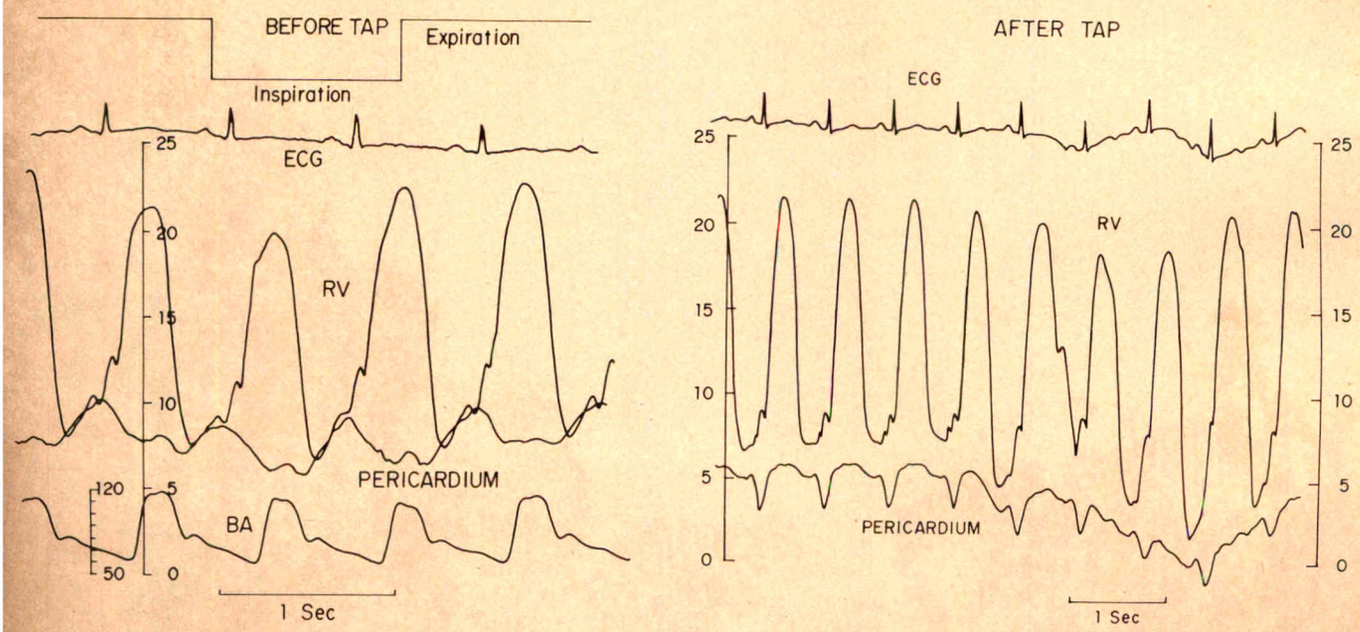


FIGURE 1. Tracings made during cardiac catheterization of a patient with early cardiac tamponade before (**left**) and after (**right**) pericardiocentesis. **Left,** from above down the electrocardiogram (ECG), right ventricular (RV) pressure, pericardial pressure and brachial arterial (BA) pressure. The phase of respiration is indicated at the top of the figure. Inspiration commences at the downslope of the square wave and expiration begins at the onset of the upstroke of the square wave. This patient does not have pulsus paradoxus, the filling pressure of the right ventricle is elevated but not excessively high and right ventricular systolic pressure is within the normal range because cardiac tamponade is not severe. Note also that intrapericardial pressure increases during isovolumic systole and relaxation and decreases during ventricular ejection. Cardiac tamponade is documented by the equilibration of diastolic pressure in the right ventricle and pericardium. **Right,** after the removal of 500 ml of pericardial fluid. Intrapericardial pressure is now significantly lower than right ventricular diastolic pressure in all phases of the respiratory cycle. The inspiratory decrease in intrapericardial pressure is now approximately 5 mm Hg compared with 2 mm Hg during tamponade. The diastolic pressure gradient between the right ventricle and the pericardium after pericardiocentesis confirms that early tamponade was present when the **left panel** was recorded. Cardiac output after pericardiocentesis increased from 3.7 to 4.9 liters/min.

throughout the cardiac cycle. Normal intrapericardial pressure is subatmospheric, nearly equal to intrapleural pressure, and decreases during inspiration. Intrapericardial pressure also shows fluctuations that are associated with the cardiac cycle. In general, the intrapericardial pressure increases when cardiac volume is greater and decreases when intracardiac volume decreases. A sharp decrease in intrapericardial pressure accompanies the X descent of the venous pressure at the onset of ejection, and this decrease rather than movement of the atrioventricular valve ring may be the cause of the X descent and of the augmentation of venous return to the heart that takes place during systole (Fig. 1). It has been pointed out that intrapericardial pressure is difficult to measure precisely, because it varies at different locations within the pericardium.[21] It is therefore necessary to level the pressure transducer to the exact hydrostatic height of the catheter tip within the pericardium.

Influence of Pericardial Dynamics on Diastolic Properties of the Ventricles

Role of pericardium on effect of nitroprusside on left ventricular pressure-volume curve: Studies of pericardial function have also been linked to the dramatic effects of nitroprusside infusion in patients with left ventricular failure. Several investigators[22] have shown that, when nitroprusside is given to patients with a large left ventricle and increased left ventricular diastolic pressure, the drug lowers the whole pressure-volume curve so that for any given diastolic volume the pressure is reduced. Several mechanisms have been proposed to explain this phenomenon. In our laboratory[10] we showed that in dogs rendered hypervolemic with infusion of dextran the phenomenon can be in large part attributed to the pericardium. We studied the dogs in the conscious state, after they had been instrumented with micromanometers, to measure left ventricular pressure, and ultrasonic dimension gauges, to reflect ventricular volume. We plotted ventricular pressure against ventricular segment length throughout the passive portion of diastole, and then infused the animals until left ventricular diastolic pressure was 25 mm Hg. A plot of ventricular pressure against segment length now showed that the whole curve had been shifted upward. When we infused nitroprusside, the pressure-segment length curve was lowered toward the control curve. In all such experiments three distinct curves were obtained: one for the control state, one after dextran infusion and another after nitroprusside infusion (Fig. 2). When we carried out the same experiments in the same animals 1 week after pericardiectomy, the results were quite different. Now dextran and nitroprusside did not shift the whole curve, but instead altered the ventricular volume and dimension in a continuous manner by extending the original curve (Fig. 2).

From these results we concluded that the elevation of the left ventricular diastolic pressure after dextran infusion and its depression by nitroprusside have many causes. When the animals were severely hypervolemic with their pericardium still intact, all the intrapericardial structures, and especially the most distensible, became acutely dilated to the degree allowed by the stiff pericardium. The resulting left ventricular diastolic pressure was the result of the influence of the other dilated intrapericardial structures and of the restraining influence of the pericardium itself. With the pericardium removed, the major determinant of ventricular diastolic pressure was the dimension of the left ventricle; therefore the diastolic pressure-dimension plot of the left ventricle was a single curve throughout the experiment, with the data points falling at the bottom of the curve in the control period, at the top of the curve after volume expansion and in intermediate locations after the administration of the vasodilator.

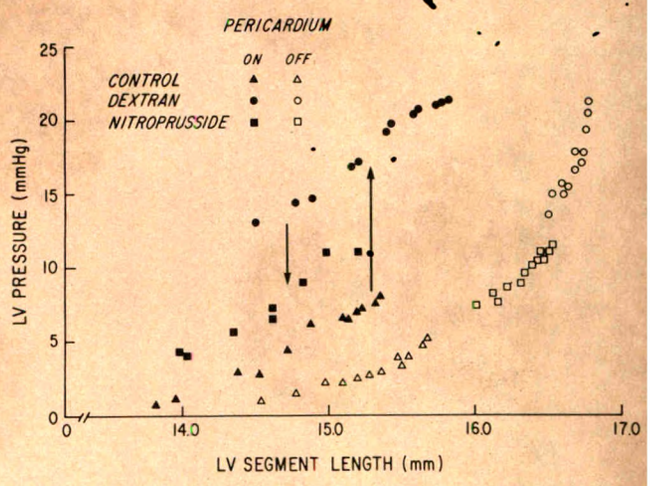


FIGURE 2. Results of a study of left ventricular (LV) pressure and the length of a segment of left ventricular myocardium throughout the passive filling period of diastole in a dog. When acute hypervolemia was induced by dextran infusion the pressure-segment length curve was shifted upward (**long arrow**). Nitroprusside shifted the curve downward toward its original position (**short arrow**). When the same experiment was performed after pericardiectomy (Pericardium *OFF*) in the same dog, hypervolemia and dextran infusion did not shift the pressure-segment length curve (**bottom curve**).

In these experiments we observed the anticipated increase in intrapericardial pressure during dextran infusion and, when we plotted left ventricular dimension against transmural ventricular diastolic pressure (left ventricular pressure minus intrapericardial pressure), the curve was the same as that obtained in dogs studied after removal of the pericardium. In this way we confirmed the importance of the pericardium in the shift of the ventricular pressure-dimension curve produced by acute manipulation of cardiac volume.

We have also studied the left ventricular pressure-volume curve in dogs in which large aortocaval shunts had been created 3 to 4 weeks previously. The dogs were studied with angiography and high fidelity pressure measurement under morphine chloralose anesthesia. The studies were performed before and after pericardiectomy. The effects of removal of the pericardium on the response of the pressure-volume curve to nitroprusside infusion in these dogs with more chronic volume overload and hypertrophy were the same as those

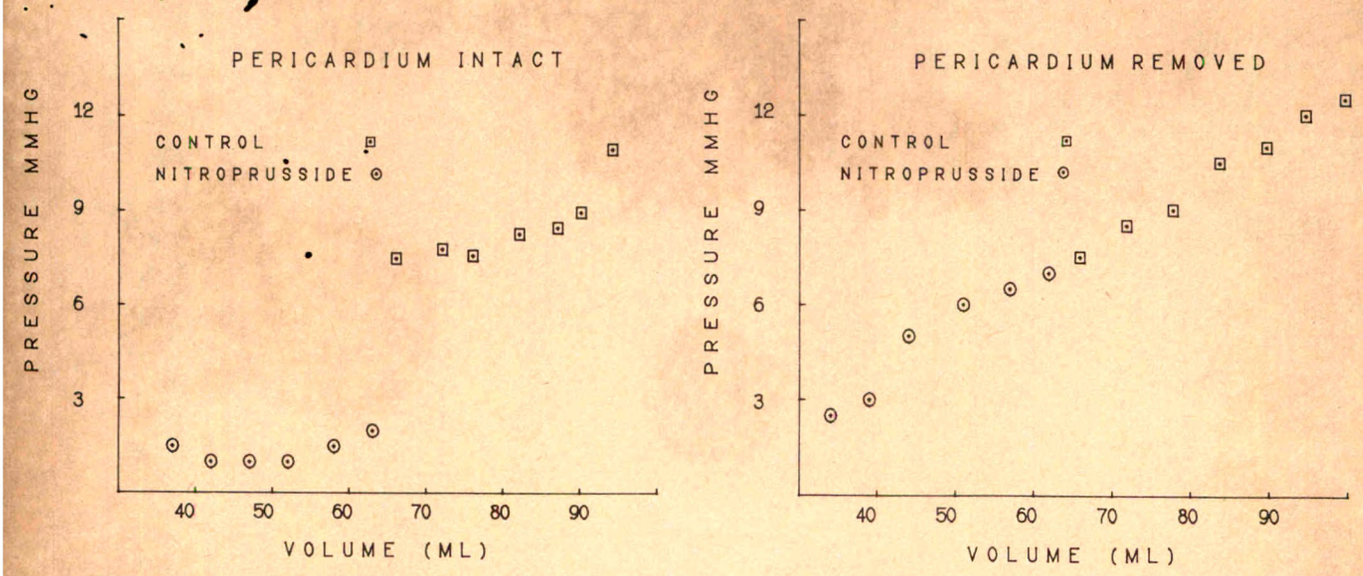


FIGURE 3. Left, left ventricular volume (obtained with angiography) plotted against left ventricular diastolic pressure throughout the passive filling phase of diastole in a dog with intact pericardium. Nitroprusside infusion shifts the pressure-volume curve downward and to the left. **Right,** after removal of the pericardium the diastolic pressure-volume curve is no longer shifted by nitroprusside. ML = milliliters; MM HG = millimeters of mercury.

observed in conscious dogs after acute volume loading (Fig. 3).

Role of pericardium in interaction between left and right ventricular pressures and volumes: Glantz et al.[23] used ultrasonic crystals implanted across various dimensions of the left ventricle and found that the main determinant of left ventricular diastolic pressure is not left ventricular dimension but right ventricular diastolic pressure. The influence of right ventricular pressure on left ventricular diastolic pressure is present both with the pericardium intact and after its removal but is much stronger when the pericardium is intact. These authors emphasize that it is no longer appropriate to consider the left ventricle a stiff unconstrained shell; it should be modeled as a relatively compliant shell restrained by the stiff pericardium.

Janicki and Weber,[24] from studies of isolated canine hearts, published evidence simultaneously with the study of Glantz et al.,[23] showing that the pericardium enhances interaction between the right and left ventricles. They also showed that when right ventricular volume was varied and left ventricular volume held constant, comparisons at any given volume in either ventricle showed that pericardiectomy reduced the diastolic pressure and the developed pressure. In contrast, when comparisons were made at equivalent end-diastolic pressures, pericardiectomy had little or no effect on end-diastolic pressure. From these results they concluded that the pericardium permits either ventricle to generate a greater isovolumic pressure from any volume.

Role of pericardium in left ventricular diastolic compliance: The results of these studies on the influence of the pericardium on ventricular diastolic pressure have considerable impact on the whole subject of ventricular diastolic compliance. There is considerable current interest in diastolic compliance of the ventricle considered as a chamber and also in the inherent compliance of the myocardium in various disease states. Several investigators are studying changes in diastolic compliance brought about by treatment—for example, replacement of the aortic valve for severe aortic stenosis with concentric hypertrophy of the left ventricle.[25] In evaluating these studies it now becomes important to consider the possible influence of the pericardium and it is desirable to know whether or not the surgeon resutured the pericardium before closing the chest. Unfortunately, except in patients with pericardial effusions, it is difficult to measure transmural ventricular pressures in the cardiac catheterization laboratory, and attempts to estimate transmural pressure by substituting esophageal pressure or using changes in pulmonary wedge or right atrial pressure are not completely satisfactory.

The abrupt increase in left ventricular diastolic pressure accompanying angina pectoris has been variously ascribed to acute cardiac failure, sudden change in ventricular diastolic compliance and incomplete ventricular diastolic relaxation induced by ischemia. It is entirely possible that the restraining influence of the pericardium contributes to this phenomenon by elevating the pressure-volume relation. Similarly, the prompt reduction in left ventricular diastolic pressure after the administration of nitroglycerin in these circumstances may reflect withdrawal of pericardial restraint when the cardiac volume shrinks in response to decreased venous return.

New Clinical Concepts of Pericardial Disease

Cardiac tamponade and pulsus paradoxus: The past year has seen several important contributions to the clinical study of pericardial disease. Reddy et al.[26]

reported their hemodynamic studies of patients with pericardial effusions and noted the important differences between patients with pericardial effusion but no cardiac tamponade, patients with uncomplicated cardiac tamponade and those with cardiac tamponade complicating severe left ventricular dysfunction manifested by high left ventricular diastolic pressure. They emphasize that when left ventricular diastolic pressure is severely elevated, equalization of left and right ventricular diastolic pressures, usually a characteristic sign of cardiac tamponade, no longer occurs. Under these circumstances cardiac tamponade is defined by equilibration of intrapericardial and right ventricular diastolic (or right atrial) pressures at an abnormally high level, but below that of left ventricular diastolic pressure. When fluid is aspirated from the pericardium, venous pressure and intrapericardial pressure decrease simultaneously while cardiac output and arterial blood pressure increase. After removal of additional quantities of pericardial fluid, the intrapericardial pressure sinks below the level of the venous pressure and little if any further hemodynamic improvement is recorded (Fig. 1).

In these patients with cardiac tamponade, pulsus paradoxus was not found. Reddy et al.[26] explain that absent pulsus paradoxus in these patients is owing to lack of inspiratory increase in right heart filling and a decrease in left heart filling with reciprocal changes in expiration. These respiratory fluctuations combined with filling of the two ventricles against a common stiffness are essential hemodynamic markers of ordinary cardiac tamponade and must be maintained if pulsus paradoxus is to be manifested. When left ventricular diastolic pressure is intrinsically elevated, filling of that chamber is determined by its compliance; therefore its diastolic pressure exceeds that of the right ventricle throughout the respiratory cycle, and pulsus paradoxus cannot appear. In atrial septal defect respiratory competition for "Lebensraum" within the pericardium is abolished by the shunt, which decreases during inspiration to balance the increase in systemic venous return. Localized collections of blood may occur after cardiac surgery and compress one side of the heart. Here again the two ventricles fill against different filling pressures and pulsus paradoxus is absent. In aortic valve incompetence (important in rupture of an aortic aneurysm into the pericardium) a major portion of left ventricular filling is independent of respiration, and pulsus paradoxus is again absent. Finally, pulsus paradoxus may be absent in extreme tamponade with severe hypotension. The practical importance of the observations by Reddy et al.[26] in patients with left ventricular disease lies in the increasing numbers of patients seen with cardiac tamponade complicating chronic renal disease and hemodialysis, a subject to which I will return at the conclusion of this paper.

Hemodynamics of cardiac tamponade: Another two papers dealing with hemodynamic considerations in pericardial disease should be mentioned. Bush et al.[27] described 19 patients with "atypical" chest pain. Cardiac catheterization in the basal state yielded normal findings but, after a large and rapid fluid challenge, features of constrictive pericarditis appeared. The authors labeled the condition occult constrictive pericarditis and sent several of the patients for pericardiectomy. Credence is lent to their hypothesis by surgical and pathologic findings consistent with chronic pericarditis, but the syndrome will have to be more clearly defined before fluid is administered in this fashion to all patients undergoing hemodynamic studies for the evaluation of chest pain.

Another paper on the hemodynamics of cardiac tamponade deals with malignant pericardial effusion.[28] The authors found eight examples of effusive-constrictive disease caused by the combination of pericardial fluid and epicardial constriction in 14 patients with malignant disease referred for pericardiocentesis; they concluded that neoplastic disease may be vying with tuberculosis as the principal cause of this syndrome.

Role of echocardiography in studying pathophysiology of cardiac tamponade: The place of echocardiography in the diagnosis of pericardial effusion and cardiac tamponade is well established and requires little general comment, although specific aspects are still being actively investigated. The echocardiogram is increasingly used not simply to evaluate the presence of effusion, but also to estimate its volume and its effects on left ventricular function. Settle et al.,[29] working in Fowler's laboratory where the pericardium has been studied for 20 years, used echocardiography to prove that during inspiration in patients with cardiac tamponade the left ventricle diminishes and the right ventricle increases in size, changes largely attributed to respiratory movement of the interventricular septum. When considering this interesting contribution to the pathophysiology of cardiac tamponade, it is necessary to recall that left ventricular diastolic dimension, stroke volume and ejection fraction decrease during inspiration and right ventricular diastolic dimension increases in normal subjects without changes in the systolic dimensions of the ventricles.[30] Schiller and Botvinick[31] demonstrated with echocardiography that right ventricular compression by pericardial effusion is a reliable sign of cardiac tamponade and is more specific for cardiac tamponade than previously proposed echocardiographic criteria, including rocking or pendular motion of the heart, pseudoprolapse or pseudo-systolic anterior motion of the mitral valve and inspiratory decline in the E-F slope of the mitral valve. This may prove to be of great physiological significance, although caution is needed in the difficult task of measuring the right ventricular dimension accurately.

Purulent pericarditis: Infectious, especially purulent, pericarditis and recurrent pericarditis continue to be obstinate therapeutic problems. The latter may require repeated courses of corticosteroids, and even pericardiectomy is not uniformly successful in terminating the attacks.

Purulent pericarditis continues to be a problem of diagnosis and management. The 88 year autopsy experience of purulent pericarditis at Johns Hopkins Hospital has recently been published.[32] The authors

compared the classic features of the 65 patients with purulent pericarditis seen since 1943 with those of 145 patients with purulent pericarditis examined from 1889 to 1943. In the later series the patients were younger and the majority were male. The most common organisms were gram-negative bacilli, Staphylococcus aureus, streptococcus and pneumococcus in that order. Spread from intrathoracic foci including those related to thoracic surgery was common. Complacency about purulent pericarditis will be removed by the observation that antemortem diagnosis was made in only 18 percent of the patients and that infection alone caused 22 percent of the deaths. The picture before 1943 was quite different. In that era purulent pericarditis was three times as frequent, afflicted the young and was secondary to pneumonia in half of the cases, with pneumococcus a frequent offender. At that time infection alone caused 86 percent of the deaths.

Purulent pericarditis is still an important cause of morbidity and mortality in children. Bacterial pericarditis was diagnosed in no less than 28 children under the age of 13 years during a 5 year period at a single hospital.[33] Staphylococcus aureus was isolated in 22 patients. The more common primary infections were osteitis and pneumonia.

Pericardial effusion in the course of hemodialysis: The proper management of pericardial effusion occurring during the course of hemodialysis remains a controversial issue in 1978. Several nephrologists[34] recommend pericardiectomy for patients with signs of pericarditis with effusion, citing the high risk of recurrent tamponade and the poor results of medical therapy with measures including administration of corticosteroids and indomethacin and increased frequency of dialysis. Other investigators[35] have claimed good results using these agents and pericardiocentesis for cardiac tamponade. Recently, the intrapericardial instillation of nonabsorbable steroids was recommended.[36,37]

Pericardial effusion recognized on routine echocardiography in hemodialysis patients in the absence of other evidence of pericarditis does not warrant therapy because it has been shown to be benign and to resolve spontaneously.[38] The effusion, which is generally smaller than 100 ml, can be detected with echocardiographic screening in about 10 percent of patients without symptoms or signs of pericardial disease who are undergoing chronic hemodialysis.[39] Hemodialysis patients with an effusion greater than 100 ml often have clinical features of pericardial disease, and this finding usually indicates new effusion.[39] The principles of treatment for pericarditis in patients undergoing hemodialysis will not be clarified without new insights into its etiology and performance of more controlled trials.

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Demonstration of the Mechanism by Which Mitral Regurgitation Mimics Aortic Stenosis

ELLIOTT M. ANTMAN, MD
GERALD H. ANGOFF, MD
LAURENCE J. SLOSS, MD

Boston, Massachusetts

A case of mitral regurgitation simulating aortic stenosis is discussed. Echocardiographic and angiographic evidence is provided demonstrating the mechanism whereby the murmur of mitral regurgitation mimics aortic stenosis. This case offers direct confirmation of the hypothesis that acoustic energy derived from a mitral regurgitant jet may be transmitted to the aorta by impingement of the jet upon the portion of the left atrial wall adjacent to the aortic root.

The murmur of mitral regurgitation is classically described as a pansystolic murmur of steady intensity that begins with the first heart sound (S_1) and ends with or after the second heart sound (S_2).[1] Characteristically the murmur is of maximal intensity at the cardiac apex and radiates to the axilla. Perloff and Harvey[2] noted that in some cases of mitral regurgitation the murmur may radiate to the upper right sternal border or interscapular area and postulated that this phenomenon was related to the orientation of the regurgitant jet. Selzer et al.[3] described a group of patients with mitral regurgitation due to ruptured posterior leaflet chordae tendineae who presented with a systolic murmur of "ejection" quality that was heard equally well at the apex and at the second right intercostal space and that in some cases radiated to the supraclavicular area. The character and location of the murmur, combined in some cases with a systolic thrill in the "aortic" area, strongly suggested aortic stenosis, which was later proved absent either at cardiac catheterization or at postmortem examination. Previous reports[4–6] also noted the confusion that may arise in differentiating mitral regurgitation from aortic stenosis on the basis of auscultatory findings alone. This report presents a case of "pure" mitral regurgitation with both echocardiographic and angiographic demonstration of the mechanism whereby this lesion may mimic aortic stenosis.

Case Report

The patient is a 68 year old man who complained of vague substernal chest pain 8 months before evaluation at the Peter Bent Brigham Hospital. He was admitted to another hospital where myocardial infarction was ruled out because of unchanged serial electrocardiograms and serum cardiac enzymes. Digitalis and diuretic drugs were administered for treatment of congestive heart failure.

A follow-up examination by the patient's physician revealed a regular pulse (92 beats/min) and a blood pressure of 130/65 mm Hg. There was no evidence of congestive heart failure. Examination of the heart revealed a grade 4/6 high-pitched crescendo-decrescendo systolic murmur that was maximal at the apex and radiated to the axilla and a grade 3/6 high pitched systolic ejection type murmur at the upper right sternal border that radiated to the supraclavicular area. The patient was referred for noninvasive evaluation with a diagnosis of mitral regurgitation and aortic stenosis.

Standard echocardiographic examination was performed using an Irex echo module with a 2.25 megahertz transducer coupled to an Irex Continutrace 101 recorder. A complete phonocardiographic study was performed using an Elema-Schonander Mingograf 81 recorder with an EMT 25C crystal microphone

From the Department of Medicine, Cardiovascular Division, Peter Bent Brigham Hospital, Boston, Massachusetts.

This work was supported in part by Training Grant HL-07049 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received April 11, 1978; revised manuscript received June 26, 1978, accepted July 5, 1978.

Address for reprints: Laurence J. Sloss, MD, Cardiovascular Division, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

and a model 1025 pulse wave transducer. Additional simultaneous echocardiographic, phonocardiographic and pulse wave recordings were obtained using the Irex multichannel recorder with echo, heart sound and pulse wave modules.

Phonocardiogram: Figure 1 is a composite of selected panels of the phonocardiogram. The heart sound recording is displayed with three channels of filtration: low frequency (center frequency 25 hertz), mid frequency (100 hertz) and high frequency (400 hertz), simultaneously recorded with appropriate pulse tracings. At all microphone locations, the phonocardiogram displays a mixed frequency crescendo-decrescendo systolic murmur with an identical time-intensity envelope. Protodiastolic (S_3) and presystolic (S_4) gallops and a short presystolic murmur are also recorded. The carotid pulse tracing is somewhat dicrotic; the upstroke is normal (t-time 0.037 second) and there is no carotid shudder. The rate-corrected ejection time is slightly shortened at 0.281 second, compatible with mitral regurgitation. The apexcardiogram discloses a faint systolic thrill coincident with the murmur; the diastolic wave form shows blunting of the rapid filling wave and a prominent *A* wave. The jugular venous tracing is normal. Thus there is no evidence of aortic valve disease, although the phonocardiogram does document the prominent occurrence of an ejection type murmur at the upper right sternal border. The mitral origin of the murmur at all locations is suggested by the absence of carotid pulse abnormality and by the presence of an apical thrill, S_3 gallop and presystolic murmur. The evidence of diminished left ventricular compliance and the crescendo-decrescendo timing of the murmur are compatible with mitral regurgitation of recent onset.[7]

Echocardiogram: The echocardiogram (Fig. 2, panel 1) discloses a normal-appearing aortic valve with normally thin and mobile leaflets that have a normal pattern of motion. The same view discloses mild enlargement of the left atrium (2.8 cm/m^2) and an abnormal mitral valve echo protruding into the left atrium during systole, posterior to the normal location of the mitral line of closure. More apically, an enlarged view of the mitral valve (Fig. 2, panel 2) shows holosystolic prolapse and excessive mobility of portions of the posterior mitral leaflet in diastole. A high frequency vibration of the echo complex arising from the posterior wall of the aortic root and the anterior left atrial wall is faintly visible in panel 1.

Figure 3 shows the expanded scale high speed echocardiographic recording of the aortic root-left atrial complex and the simultaneously recorded right upper sternal border and apex

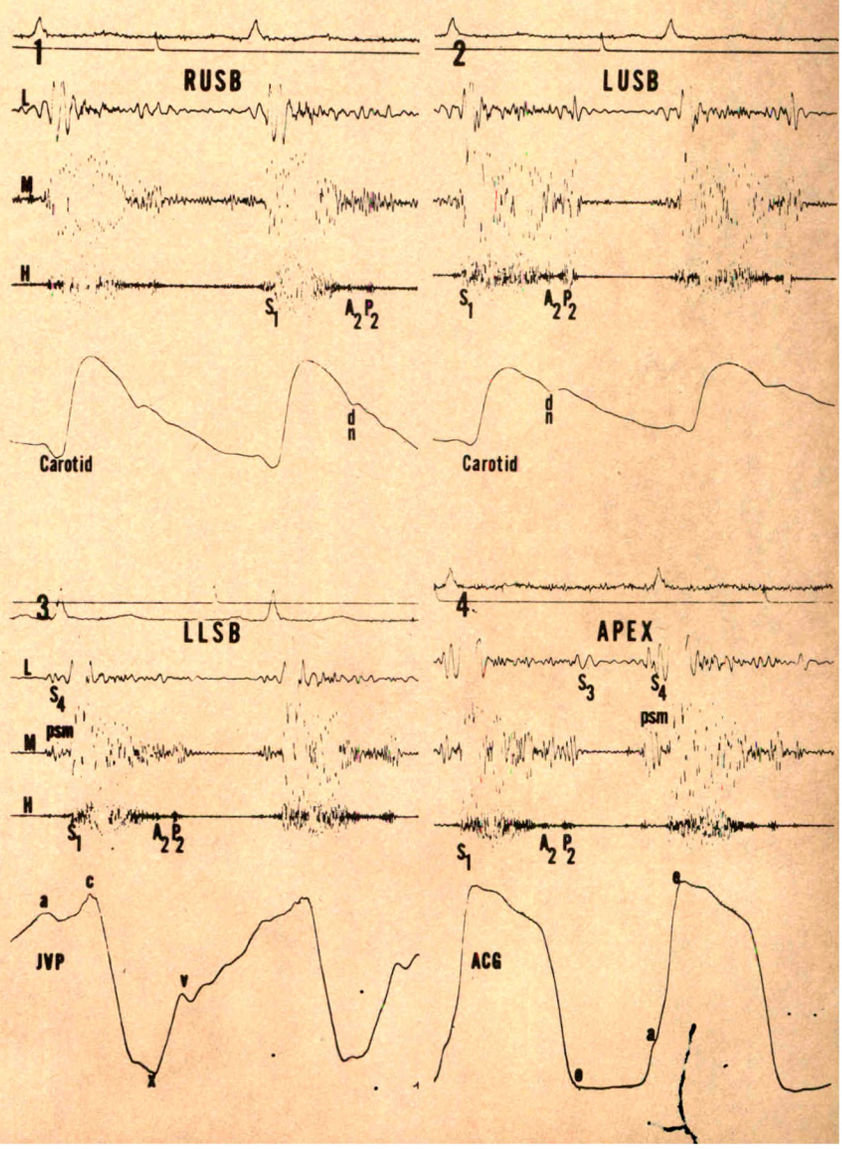


FIGURE 1. Composite of four panels from the phonocardiogram (see text for description). A_2 = aortic component of the second heart sound; ACG = apexcardiogram; dn = dicrotic notch of the carotid arterial pulse tracing; JVP = jugular venous pulse tracing; LLSB = left lower sternal border; L, M and H = low, medium and high frequency phonocardiographic channels, respectively; LUSB = left upper sternal border; P_2 = pulmonary component of the second heart sound; psm = presystolic murmur; RUSB = right upper sternal border.

phonocardiograms and the carotid pulse tracing. These recordings demonstrate prominent high frequency vibration of structures comprising the posterior aortic/anterior left atrial region; the echocardiogram shows systolic "break-up" of the trace of these structures in contrast to the "solid" lines of other areas; this region also appears solid during diastole. As before, the simultaneously recorded right upper sternal border and apex phonocardiograms show identity of the time-intensity envelope of the murmur at these two locations, and the carotid pulse shows no evidence of aortic stenosis. The study demonstrates the onset of vibration of the aortic-left atrial complex, with the latter portion of the first heart sound occurring more than 20 msec before the onset of carotid upstroke and continuing through the second heart sound. Further enlargement of the aortic root echo in Figure 4 shows that the vibrating structure is located outside the aortic lumen and is

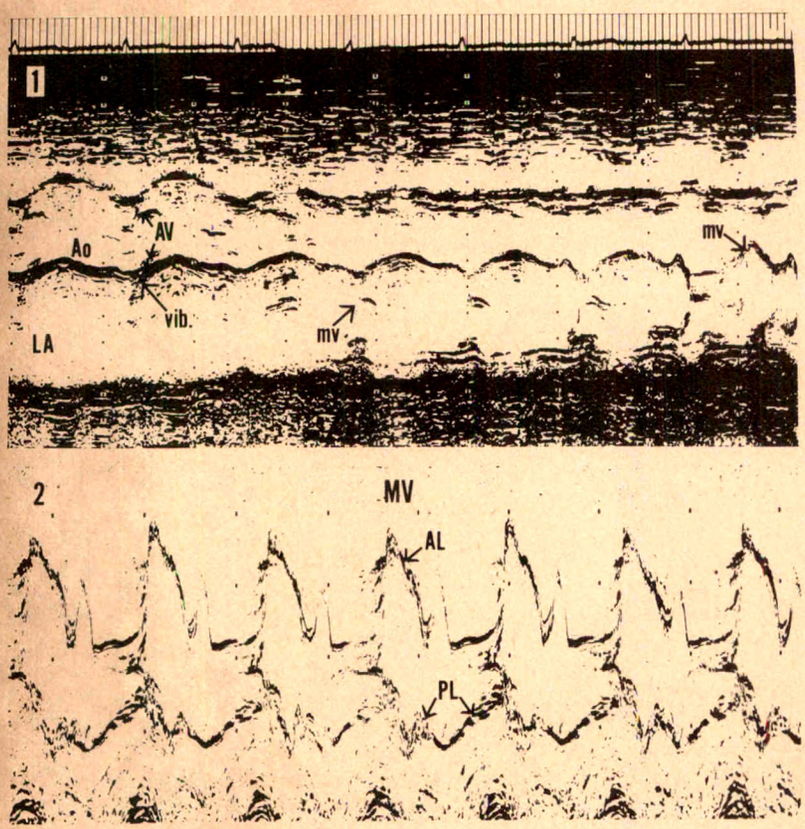


FIGURE 2. Panel 1, echocardiographic sweep from the aortic root (Ao) on the left toward the apex of the left ventricle on the right (see text). **Panel 2,** enlarged echocardiographic view of the mitral valve (MV). AL = anterior mitral leaflet; AV = aortic valve leaflets; LA = left atrium; PL = posterior mitral leaflet; vib. = systolic vibration of the aortic root (see text).

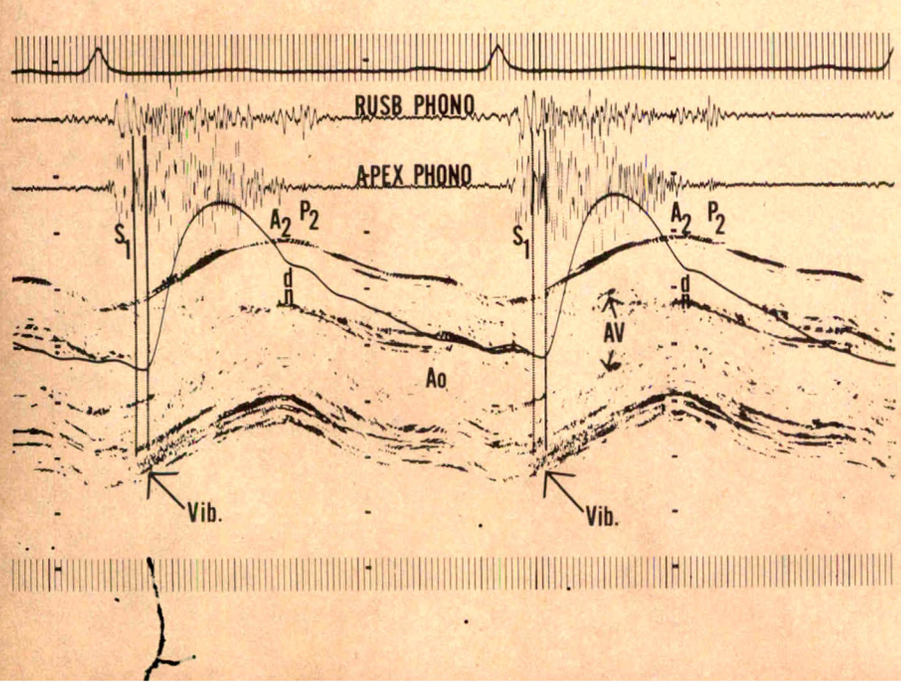


FIGURE 3. Expanded scale high speed echocardiographic recording of the aortic root-left atrial echo complex with simultaneous right upper sternal border (RUSB) and apex phonocardiograms (PHONO) and carotid pulse tracing. The **vertical lines** mark the onset of systolic vibration (Vib.) and of the carotid upstroke. Abbreviations as in Figures 1 and 2.

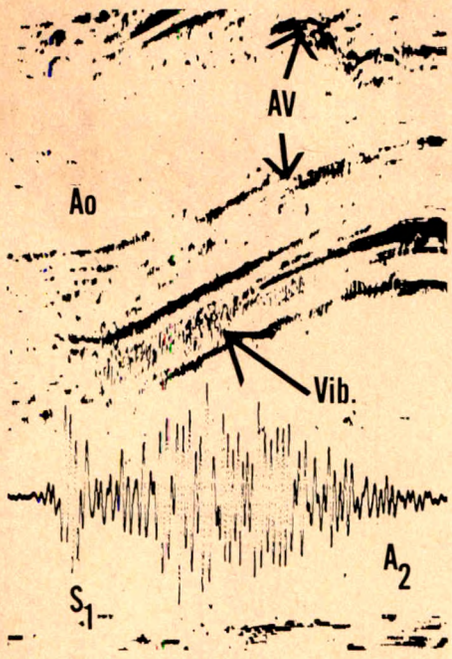


FIGURE 4. Enlarged view of the aortic root. High frequency systolic vibrations (Vib.) external to the lumen of the aortic root (Ao) are not associated with the aortic valve (AV) apparatus.

not associated with the aortic valve apparatus; the timing of the vibrations is inconsistent with an ejection phase phenomenon but consistent with a relation to a holosystolic event.

Cardiac catheterization: The findings confirmed the presence of pure mitral regurgitation with regurgitant waves reaching 90 mm Hg in the pulmonary capillary wedge tracing. There was no evidence of an aortic valve pressure gradient. Left ventricular angiography performed in the right anterior oblique projection (Fig. 5), demonstrated a superiorly oriented mitral regurgitant jet. Analysis of the entire cine sequence revealed that the jet was directed toward the aortic root.

Operative findings: The mitral valve was visualized with a left atriotomy posterior to the interatrial groove on the right side. The valve leaflets were remarkably large and redundant. The chordae tendineae were thin, delicate and elongated, with no fusion. All of the chordae tendineae toward the medial half of the posterior leaflet were ruptured, and the free edge of the leaflet was entirely flail in a fashion that could easily direct a jet from the left ventricle toward the medial wall of the left atrium at the site of the aortic protuberance. The papillary muscles and the aortic valve appeared normal. Pathologic examination revealed no calcification or evidence of vegetation on the mitral valve; areas of focal myxomatous degeneration were noted grossly and microscopically. The mitral valve was replaced with a stented porcine aortic valve bioprosthesis.

An echocardiogram performed 3 months postoperatively (Fig. 6) showed a decrease in the size of the left atrium and absence of the previously noted systolic vibrations of the posterior aortic wall.

Comment

Mechanism by which mitral regurgitation might mimic aortic stenosis: Perloff and Harvey[2] and Selzer et al.[3] both proposed that a rightward and anterosuperiorly directed regurgitant jet might arise from the hood-like deformity of a posterior mitral valve leaflet with disrupted chordal support. A jet with this orientation might cause the systolic murmur to radiate in a fashion closely resembling that of aortic stenosis. Two basic types of evidence have been presented to support this theory. First, fibrous patches have been visualized on the left atrial wall where the regurgitant jet presumably impinged on the endocardium.[3,6] Second, a palpable systolic thrill has been noted in the "aortic" area[3] over the left ventricular outflow tract during surgery[4] and in the upper atrial septum during the en-

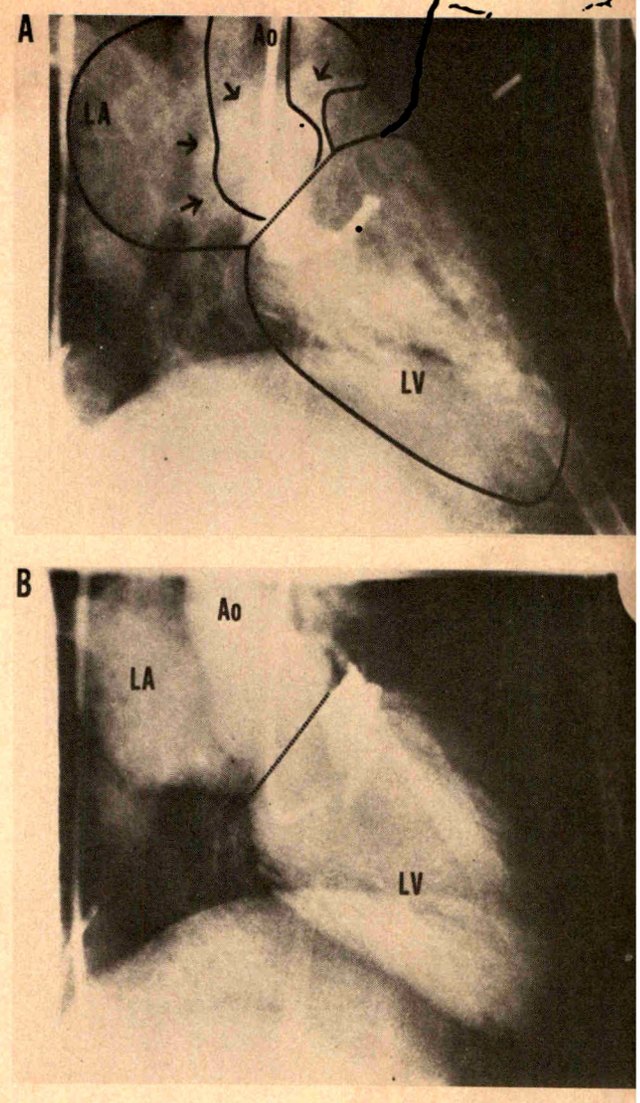


FIGURE 5. Early **(A)** and late **(B)** systolic angiographic frames from power injection of contrast medium into the left ventricle. **Solid lines** in **A** delineate boundaries of the left ventricular (LV) and left atrial (LA) chambers as determined from a later cine frame of the same injection **(B).** The **arrows** indicate the prolapsing posterior mitral leaflet and anterosuperior orientation of the regurgitant jet located just posterior to the position of the aortic root (Ao), also determined from the later frame **(B).**

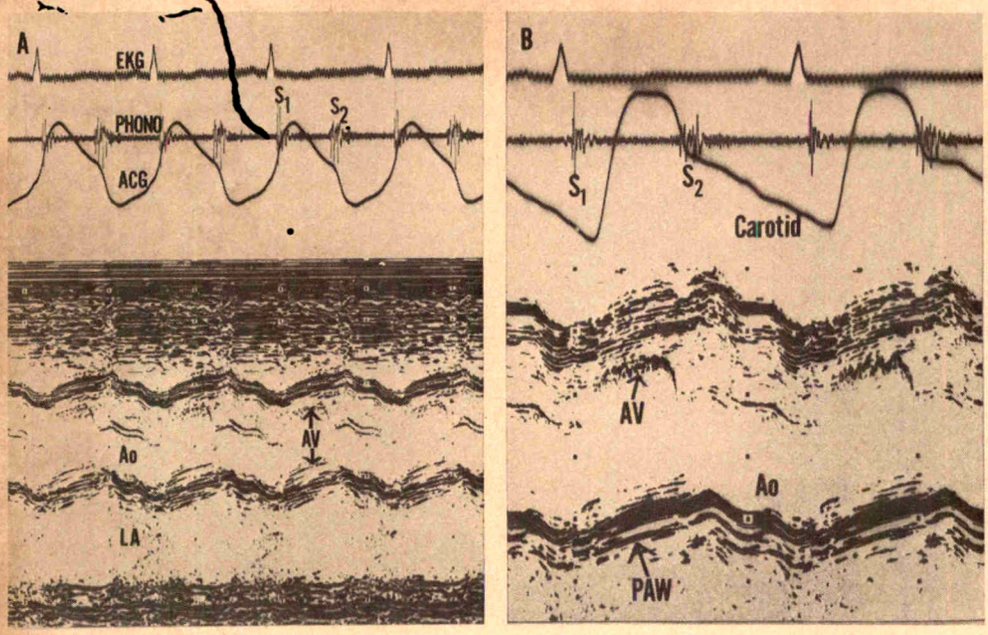


FIGURE 6. Postoperative echocardiogram. **A,** view of the aortic root (Ao) and valve (AV) and the left atrium (LA) with simultaneous apexcardiogram (ACG) and right upper sternal border phonocardiogram (PHONO). The systolic murmur is no longer present, the apexcardiogram has become normal and the left atrium is smaller. **B,** enlarged view of the aortic root with simultaneous carotid arterial pulse tracing and right upper sternal border phonocardiogram. Systolic vibration of the posterior aortic wall (PAW) is no longer present.

gagement of a transseptal needle at cardiac catheterization.

Evidence of impingement of regurgitant jet on left atrial wall adjacent to aorta: This is a typical case of demonstrably "pure" mitral regurgitation that in some ways may simulate at least the auscultatory findings of aortic stenosis. The possibility of aortic stenosis was excluded with noninvasive means and cardiac catheterization, and mitral regurgitation due to posterior mitral leaflet chordal rupture was convincingly demonstrated. As noted earlier, this constellation of findings is not unique. What is unique is the recording of vibration of the posterior surface of the aortic root, providing direct confirmation of the hypothesis that acoustic energy derived from a mitral regurgitant jet may be coupled and transmitted to the aorta by impingement of the jet on that portion of the left atrial wall adjacent to the aortic root.

Acknowledgment

The assistance of John J. Collins, Jr., MD and Priscilla Peters is gratefully acknowledged.

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Atypical Ventricular Tachycardia as a Manifestation of Disopyramide Toxicity

RICHARD S. MELTZER, MD
EDWARD W. ROBERT, MD
MAUREEN McMORROW
RANDOLPH P. MARTIN, MD

Stanford, California

An unusual ventricular tachyarrhythmia developed in a 57 year old woman with recurrent ventricular tachycardia and toxic disopyramide plasma concentrations. The rhythm was similar to the patient's previous ventricular tachycardia, but the rate was slower and the QRS complex was markedly widened, mimicking the electrocardiographic changes associated with electrolyte abnormalities. Disopyramide, which has electrophysiologic properties similar to those of quinidine, probably caused the arrhythmia and should be added to the list of drugs associated with atypical ventricular tachycardia.

Disopyramide phosphate (Norpace®), a new antiarrhythmic agent, has recently been released for use in treating ventricular arrhythmia. Although structurally distinct from other antiarrhythmic drugs, it is classified as a type I agent, and its electrophysiologic properties are similar to those of quinidine.[1–4] QRS widening has been noted as an effect of disopyramide,[4] but atypical ventricular tachycardia has not been reported with its use. We report a case of disopyramide toxicity associated with an atypical ventricular tachycardia and include a brief discussion of the tachycardia.

Case Report

A 57 year old white married woman was admitted to Stanford University Hospital on October 5, 1977 with a diagnosis of phenytoin toxicity. She had been well until January 1977, when she began having symptomatic ventricular tachycardia requiring multiple drugs or direct current cardioversions, or both. Previous coronary arteriograms from another hospital disclosed severe coronary disease with a poorly contracting left ventricle and a left ventricular end-diastolic pressure of 22 mm Hg. The patient's first evaluation at Stanford University Hospital was in February 1977. At that time her blood pressure was normal. Bibasilar rales and a fourth sound gallop were present. A grade 2/6 holosystolic high pitched murmur was heard at the apex.

The electrocardiogram (Fig. 1 [2/2/77]) revealed normal sinus rhythm at a heart rate of 65 beats/min with occasional unifocal premature ventricular complexes and nonspecific ST-T wave abnormalities. The P-R interval was 0.16 second, the QRS duration 0.09 second and the Q-T_c interval 0.49 second. The chest X-ray film showed cardiac enlargement and pulmonary vascular redistribution consistent with congestive heart failure. Ambulatory electrocardiographic monitoring for 24 hours revealed multifocal premature ventricular complexes, frequent trigeminy, R on T phenomenon and two sustained runs of ventricular tachycardia.

During an intracardiac electrophysiologic study, ventricular tachycardia was repeatedly induced with single right ventricular premature stimuli; procainamide provided no prophylaxis. The study was based on a diagnostic and therapeutic rationale similar to that described by Fisher et al.[5]; additional findings included normal resting conduction intervals (A-H interval 115 msec and H-V interval 45 msec) and normal atrial and atrioventricular (A-V) nodal refractory periods in normal sinus rhythm. On February 6, 1977 the patient

From the Cardiology Division, Stanford University School of Medicine, Stanford, California. This work was supported in part by Grant HL-5866 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received February 13, 1978; revised manuscript received June 28, 1978, accepted July 5, 1978.

Address for reprints: Edward W. Robert, MD, Cardiology Division, Stanford University School of Medicine, Stanford, California 94305.

underwent quadruple coronary bypass graft surgery. During the next 6 months she had frequent episodes of ventricular tachycardia (Fig. 2) that were refractory to procainamide, quinidine, small dose propranolol and disopyramide (150 mg orally, every 4 hours). Intolerance to procainamide and quinidine developed.

In September 1977 the patient was admitted to Stanford University Hospital for further evaluation of recurrent ventricular tachycardia. During a second electrophysiologic study, ventricular tachycardia could again be easily induced with right ventricular pacing and was not abolished by lidocaine or overdrive pacing. The administration of lidocaine did

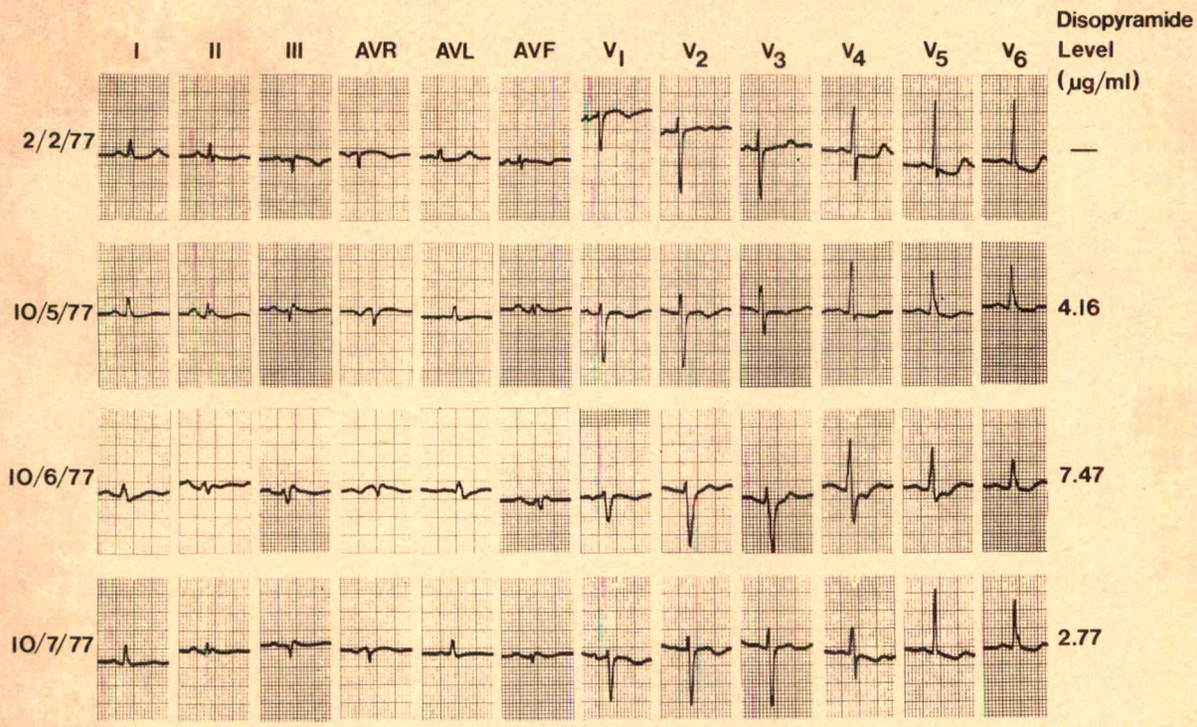


FIGURE 1. Twelve lead electrocardiograms recorded on the patient's first admission to Stanford (2/2/77), her third admission (10/5/77), a half hour after reversion of the bizarre rhythm shown in Figure 3 (10/6/77) and the following day (10/7/77). Concomitant disopyramide phosphate plasma levels are shown. Note the progressive P-R prolongation (0.17 to 0.23 second), QRS widening (0.07 to 0.14 second) and constant Q-T_c prolongation (0.49 to 0.52 second) from February 2 to October 6, 1977 with improvement on October 7 with the lower serum disopyramide level.

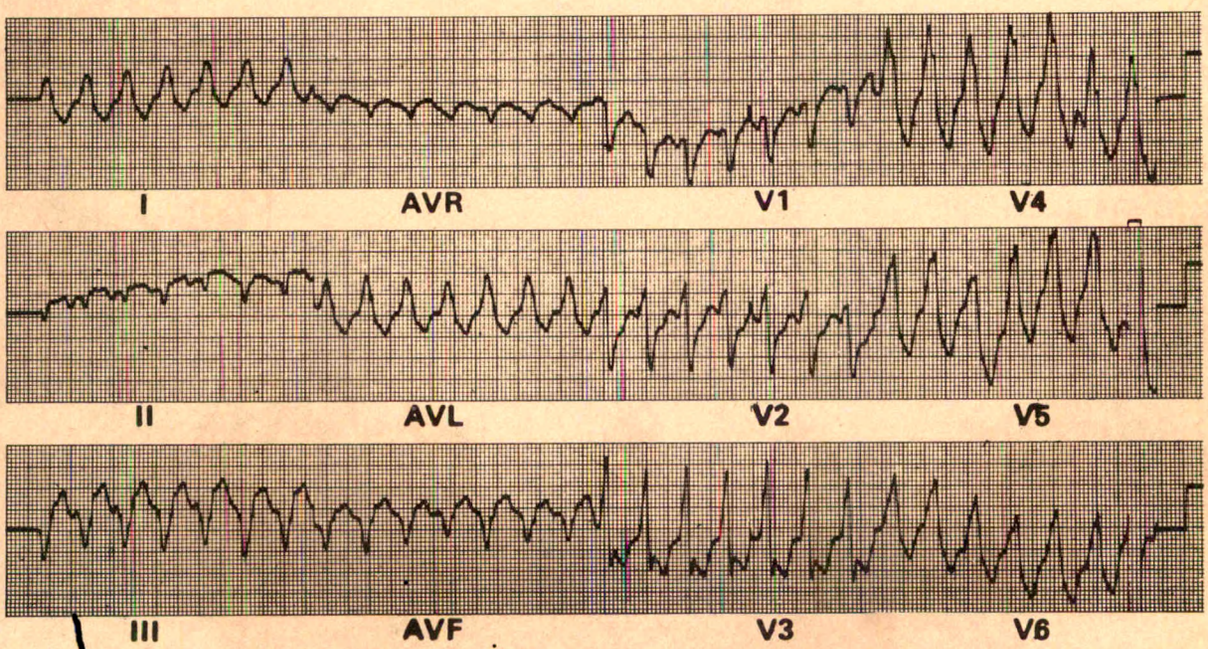


FIGURE 2. Twelve lead electrocardiogram during ventricular tachycardia in September 1977.

not alter the ability to induce tachycardia; however, after a total oral dose of 600 mg of disopyramide, the ventricular tachycardia could no longer be induced, suggesting that chronic administration of disopyramide might prevent ventricular tachycardia. The patient was maintained on a regimen of disopyramide, 300 mg every 6 hours, but because of repeat episodes of ventricular tachycardia in the following days, phenytoin was added to the regimen. On September 29, while the patient was taking phenytoin and disopyramide, repeat electrophysiologic studies were performed, and the arrhythmia could not be induced. The patient was then discharged on a regimen of phenytoin, 100 mg every 6 hours, and disopyramide, 300 mg orally every 6 hours.

Five days later the patient was admitted to Stanford Hospital with slurred speech, difficulty in walking and a plasma phenytoin level of 35 μg/ml. The admission electrocardiogram is shown in Figure 1 (10/5/77). The initial diagnosis was phenytoin toxicity, and administration of the drug was discontinued. Disopyramide was continued, but the dose was inadvertently increased to 600 mg orally every 6 hours, twice

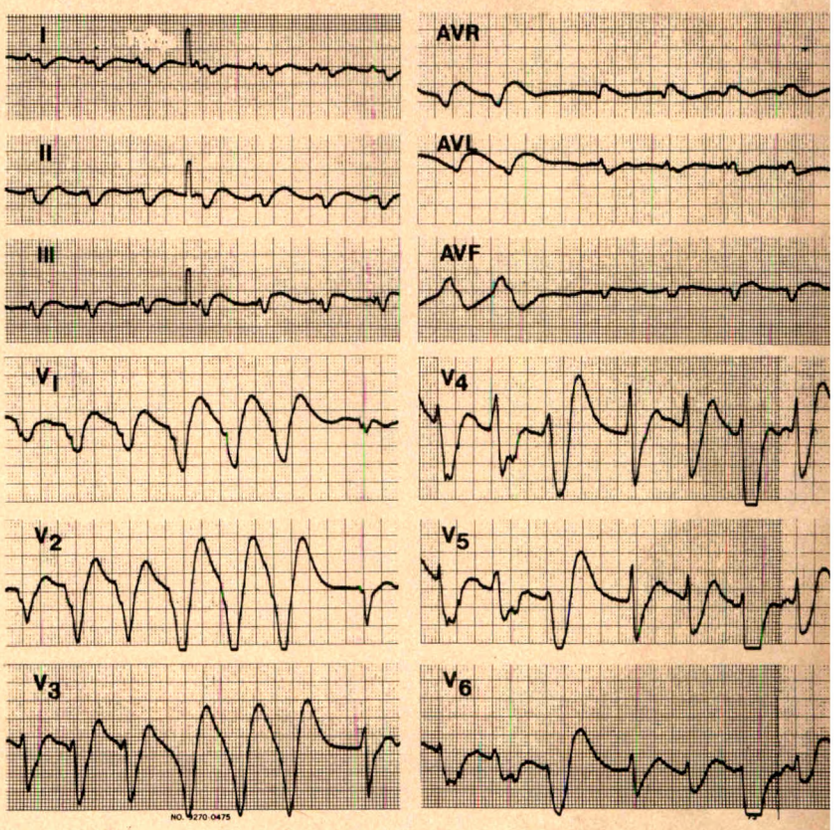


FIGURE 3. Twelve lead electrocardiogram during the bizarre rhythm that continued for 1 1/2 hours on October 6, 1977. The three leads in each grouping were recorded simultaneously.

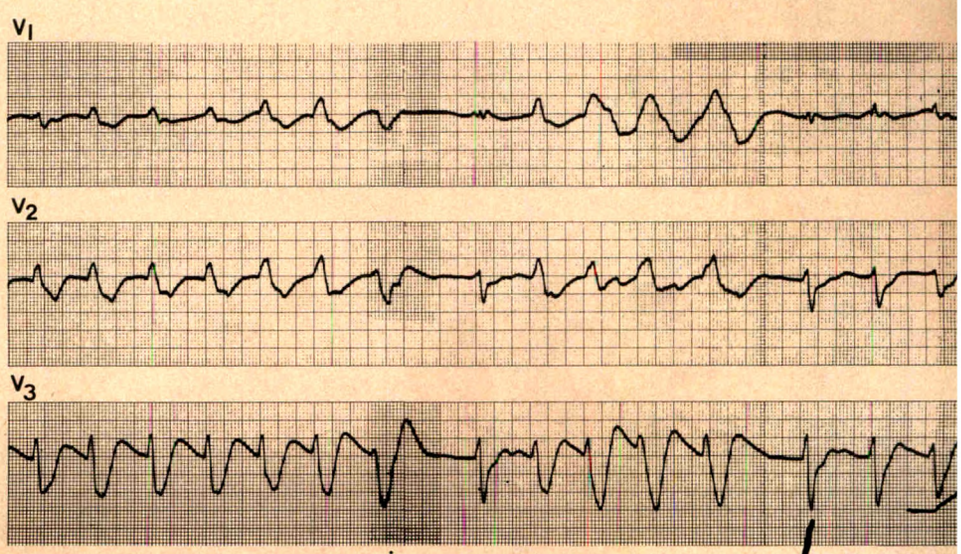


FIGURE 4. Simultaneous lead V_1, V_2 and V_3 rhythm strips during the arrhythmia shown in Figure 3.

the patient's normal dose. One day later a bizarre rhythm suddenly developed, with a wide QRS complex that was believed to be a slower version of the patient's recurrent ventricular tachycardia (Fig. 3 and 4). At this time, the electrolytes were normal (potassium 4.5 mEq/liter; magnesium, 1.4 mEq/liter), and the phenytoin level was 31 μg/ml (therapeutic level, 10 to 20 μg/ml). The disopyramide level was 7.5 μg/ml (therapeutic level, 3 to 6 μg/ml; Meffin et al., unpublished data). Disopyramide was withheld and normal sinus rhythm returned (Fig. 1, 10/6/77 and 10/7/77).

The administration of a smaller dose of disopyramide was started, and the patient has had no documented recurrence of ventricular tachycardia since hospital discharge. The administration of phenytoin has not been resumed.

Discussion

We believe that this patient's arrhythmia represents a variant of ventricular tachycardia and that it was induced by disopyramide toxicity. Although its origin was not documented with intracardiac electrophysiologic studies, the arrhythmia was probably a variant of ventricular tachycardia because (1) the patient had previously had frequent documented episodes of ventricular tachycardia, (2) the atypical rhythm, although slower and with wider QRS complexes, had a configuration similar to that of the patient's typical ventricular tachycardia, and (3) no P wave activity was evident.

Alternative explanations for this rhythm include atrial fibrillation with varying degrees of aberrant conduction and accelerated idioventricular rhythm with intermittent ventricular capture from a supraventricular focus. These explanations are unlikely because (1) no P wave or fibrillation wave activity was identified in the surface electrocardiogram; (2) the aberrancy of supraventricular beats to this extent is unlikely because the sinus rhythm immediately before and after showed only minimal QRS prolongation at a similar ventricular rate; and (3) the QRS configuration was constantly changing, a phenomenon not seen in accelerated idioventricular rhythms. It is possible that some of the narrower QRS complexes, despite a lack of surface P waves, reflect intermittent capture; this is consistent with both typical and atypical ventricular tachycardia. The extremely wide QRS complexes mimicked the electrocardiographic changes associated with electrolyte abnormalities (hypokalemia or hypomagnesemia), but both serum values were normal at the time (potassium 4.5 and magnesium 1.4 mEq/liter).

Disopyramide toxicity as a cause of ventricular tachycardia: Disopyramide, with electrophysiologic properties similar to those of quinidine,[1–4] was probably the cause of this arrhythmia. Toxic plasma levels of disopyramide were documented when the atypical ventricular tachycardia was recorded. Quinidine has long been known to be associated with syncope due to paroxysmal ventricular tachycardia and fibrillation,[6,7] generally in conjunction with Q-T prolongation. Disopyramide was recently implicated in a similar case of repetitive ventricular tachycardia.[8] Both drugs were shown to prolong ventricular refractory periods and decrease myocardial conduction velocity. These effects, which were evident in our patient's baseline electrocardiogram before the bizarre arrhythmia, included prolongation of the P-R, QRS and Q-T intervals. The electrocardiographic changes ran parallel to the disopyramide plasma concentrations. Disopyramide has been reported to slow the rate of ventricular tachycardia in some patients,[9] and this phenomenon may explain the relatively slow rate of atypical ventricular tachycardia in our patient.

It is unlikely that phenytoin toxicity caused this rhythm because it tends to shorten QRS duration and speed ventricular conduction[10,11] and has not been associated with a bizarre ventricular rhythm.

Features of atypical ventricular tachycardia: The unusual features of our patient's arrhythmia (variation in QRS configuration marked QRS widening) are in some ways similar to those of other atypical ventricular tachycardias. These rhythms have been variously termed "repetitive paroxysmal tachycardia,"[12] "torsade de pointes"[13,14] and "cardiac ballet."[15] Their distinctive features are a continuous variation of QRS configuration and repetitive sequences of multiform ventricular complexes, often occurring in the presence of drug toxicity or electrolyte abnormalities causing Q-T prolongation.

Disopyramide at toxic plasma levels appears to be a cause of an atypical ventricular tachycardia, probably as a result of its quinidine-like electrophysiologic properties. With the increasing use of disopyramide, clinicians should be aware of this potential toxic manifestation.

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EDITORIALS

Torsade de Pointes: An Addition to the Nosography of Ventricular Tachycardia*

CHARLES E. KOSSMANN, MD, FACC

Memphis, Tennessee

The article by Meltzer, Robert, McMorrow and Martin, which appears in this issue of the Journal,[1] describes an "atypical" ventricular tachycardia occurring after toxic doses of disopyramide (Norpace®). Together with two other reports of single examples of ventricular tachycardia going on to ventricular fibrillation as a result of oral or intravenous use of disopyramide,[2,3] it serves to alert the clinician to the potential hazards of this drug. Pertinent to the remarks that follow, the paper also stimulates interest in the differentiation of "typical" from "atypical" ventricular tachycardia and the possible clinical usefulness of an expanded and detailed nosography of ventricular rhythms on the basis of frequency, form, sequence and direction of the electrocardiographic ventricular complexes.

Atypical Ventricular Tachycardias: Classification

Among the atypical forms of ventricular tachycardia, until recently rarely mentioned in American publications, Meltzer and his colleagues cite repetitive paroxysmal tachycardia,[4] cardiac ballet[5] and torsade de pointes.[6] In an effort to categorize the records shown in their article into one of these types, it will be noted that the original tachycardia for which therapy was prescribed displayed a regular rate of 160/min, a constant form of the ventricular deflections simulating left bundle branch block, a frontal plane axis of approximately −45°, a QRS interval of 0.16 second and evidence of retrograde conduction on a 1:1 basis (leads III and aVF). These findings suggest an ectopic focus to the right of and below the center of the total mass of excitable ventricular muscle (if junctional tachycardia with left bundle branch block or retrograde junctional conduction with ventricular reentry through an otherwise "hidden" right-sided anomalous pathway can both be ruled out). During the toxic rhythm from the disopyramide, the ventricular rate is 93/min, the QRS interval 0.24 second and there are recurrent progressive changes in magnitude and form with slight further widening of the QRS deflections until, over a period of four or more beats, the rhythm seems to stop with a delayed interjection of what appears to be a widened supraventricular beat. However, no evidence of supraventricular electrical activity can be found. There is some variation from this described pattern but, all in all, the record seems to fit best the rhythm described as cardiac ballet[5] with a slow ventricular (idioventricular) focus intermittently encountering progressive refractoriness of the ventricles, a kind of global ventricular Wenckebach phenomenon, with eventual failure of intraventricular conduction (dropped ventricular beat).

This interpretation is, of course, speculative. It could have been less so if intracardiac electrographic studies had been made, a procedure difficult to justify in view of the well known propensity of the cardiac catheter to produce ventricular arrhythmias by itself.[7] Nevertheless, the case supports the contention that additional clinical and electrophysiologic information is needed on arrhythmias of infrajunctional origin, and that it could be obtained by closer attention to the ordinary electrocardiographic appearance of ventricular rhythms and tachycardias as well as by obtaining the maximal amount of electrophysiologic data possible with currently available techniques.

Most of the efforts toward a further understanding of ventricular arrhythmias have been made by French

From the Department of Medicine, University of Tennessee College of Medicine, Memphis, Tennessee. Manuscript received August 14, 1978; revised manuscript received September 19, 1978, accepted September 27, 1978.

Address for reprints: Charles E. Kossmann, MD, Department of Medicine, University of Tennessee, Memphis, Tennessee 38163.

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

and English investigators. American publications have been surprisingly devoid of attention to the electrocardiographic details of these abnormal rhythms, possibly because of the general attitude that such studies would not be productive. Further, there seems to have been for some time a feeling among American electrocardiographers that the diagnosis of ventricular tachycardia cannot always be made with confidence without at least the availability not only of intracardiac leads but also of clinical and acoustical data.[8]

In earlier nosologic endeavors, the rate of the abnormal rhythm, in addition to morphologic features has not been neglected in such usually benign phenomena as idioventricular (or ventricular) rhythm with a ventricular rate of less than 50 beats/min and accelerated ventricular rhythm in which the rate may approach 100 beats/min. Similarly, it has not been neglected in the serious rhythm called ventricular flutter where a rate may be 300 or more beats/min. Alternate change in configuration of the QRS complex and T wave has been the basis of the diagnosis of bidirectional tachycardia and, although the ventricular origin of the arrhythmia has been challenged at various times, intracardiac electrography has demonstrated its infrajunctional origin.[9]

The attempts at further subclassification into "atypical" forms probably began with Gallavardin[10] in 1922 and his clinical differentiation of recurrent short paroxysms of ventricular (and other) tachycardias from the usual ominous prefibrillatory kind. He called the former arrhythmia "tachycardie en salves." Wilson and his associates[11] collected several isolated reports of similar cases and, in addition, described four cases of their own of ventricular tachycardia in young persons (respectively aged 25 and 31 years, "in the 30's" and 52 years) induced by exertion without evidence of organic heart disease although one patient, a 31 year old man, died suddenly. Parkinson and Papp[4] published a complete review of this kind of rapid heart action in 1947, and added 40 cases of their own, of which 9 showed ventricular tachycardia. They called the arrhythmia "repetitive paroxysmal (ventricular) tachycardia" and indicated that others before them had described it with such adjectives as intermittent, incessant, chronic and habitual. It was, for the most part, refractory to treatment but benign, occurring in persons, including children, without other evidence of heart disease, often persisting over a period of years and subsiding spontaneously. The fact that published records of this type of ventricular tachycardia show an initiating beat with a form similar to or identical with subsequent beats, and spontaneous variations in rate without change in form, makes it likely that a single ectopic focus is the source of this kind of ventricular tachycardia.

Cardiac ballet, described by Smirk and Ng[5] in 1969, is similar to repetitive paroxysmal ventricular tachycardia except that the replicated patterns of the QRS complexes are multiform, may or may not be interspersed with sinus beats and frequently presage ventricular fibrillation. Adjacent abnormal beats may be bidirectional, but there are no clusters of complexes pointing in one direction and then the other from the baseline.

Torsade de Pointes

Torsade de pointes was first described and named by Dessertenne.[6] "Twisting of the points" characterizes the configuration of the complexes quite well in that the principal widened QRS deflection changes cyclically from a summit to a nadir and back, with the recovery deflections, usually more rounded, in the opposite direction to the "points" (QRS). The "envelope" of the record forms a kind of modulated sine wave of variable pattern. On inspection of the few published records the impression gained is that two ventricular foci, as suggested by Dessertenne, are operative and slightly out of phase, tending to synchronize (a bifocal ventricular "accrochage"), with first one and then the other controlling the ventricles, suggesting stimulation by both foci but to a gradually changing and variable extent. The narrower and smaller QRS complexes at the "nodes" of the "spindles" may represent a more or less simultaneous discharge of the foci in both ventricles to yield a QRS complex of near supraventricular form. Other explanations undoubtedly can be given such as block in one fascicle (usually the right bundle branch) with progressive, as opposed to alternate, impaired conduction in one of the other two with a single pacing focus probably in the ventricles.[9] It might also represent a prolonged undulatory phase of ventricular fibrillation.[1] An electrophysiologic feature of significance is that a sequence seems to be initiated by a late, rather than early, R on T premature complex[13] suggestive of a delayed vulnerable period.

Criteria for the electrocardiographic diagnosis of torsade de pointes are not well established. This has already resulted in a rather indiscriminate use of the tantalizingly euphonius French term for rapid ventricular rhythms that have "many" of the electrocardiographic features of Dessertenne's arrhythmia. In the first paper by American authors[14] in which the term is used in the title to indicate it as a complication of prolonged use of a liquid protein diet, the one example shown has more the appearance of the undulatory phase of ventricular fibrillation than of torsade des pointes. Another electrocardiogram described in the text, but not shown, seems more characteristic in configuration. Krikler and his colleagues,[13,15] who have studied this rhythm more than anyone else, state that many examples have been published under other guises, but a search is not too rewarding if rigid criteria for the diagnosis are applied.

As a start in the direction of precise definition it is suggested that the electrocardiogram must show a true twisting of the points, that is, a complete reversal of the QRS and T deflections, and that this should occur progressively yielding a modulated sine curve with QRS complexes of small size and possibly normal widths at those portions of the curve that have the least amplitude (the "nodes"). As observations increase in this apparent rhythmic transition between ventricular tachycardia and ventricular fibrillation, additional criteria relative

to rate, sequence and form may be added. As an aid to this objective it would be desirable to record all ventricular arrhythmias at a paper speed faster than 25 mm/sec.

The question arises as to whether torsade de pointes can be classified as a ventricular tachycardia or is, in truth, the earliest phase of ventricular fibrillation to which it often progresses. Wiggers[12] described experimental ventricular fibrillation as occurring in four stages: undulatory (1 to 2 seconds), convulsive (15 to 40 seconds, 600 to 750 oscillations/min), tremulous (2 to 3 minutes, 600 to 1,000 oscillations/min and atonic. Although the undulatory stage was very brief, he concluded from simultaneous cinematographic observations that it started as a single premature contraction with the following complexes representing reentrant waves of large size that at least on the surface did not follow the same path or area. As noted, some of the published records of rhythms called torsade des pointes appear to show rather the undulatory phase of ventricular fibrillation. Further careful clinical observations after a reading of Wiggers' meticulously made studies may clarify this point.

Etiology and Treatment

The causes and treatment of torsade de pointes have been well covered by Krikler and Curry.[13] The predominant underlying causes are those that prolong the Q-T interval; this favors the basic mechanism as being nonuniform prolongation of refractory period rather than enhanced rhythmicity or excitability. These causes include atrioventricular block,[16] hypokalemia,[17] hypomagnesemia,[18] surdocardiac syndromes,[19] quinidine-like drugs,[20] psychotropic drugs, cardiac ischemia and myocarditis. Perhaps mitral valve prolapse should be added to the list because the ventricular tachycardia seen with it is refractory to conventional drug therapy. However, a documented example has not yet been reported.[21]

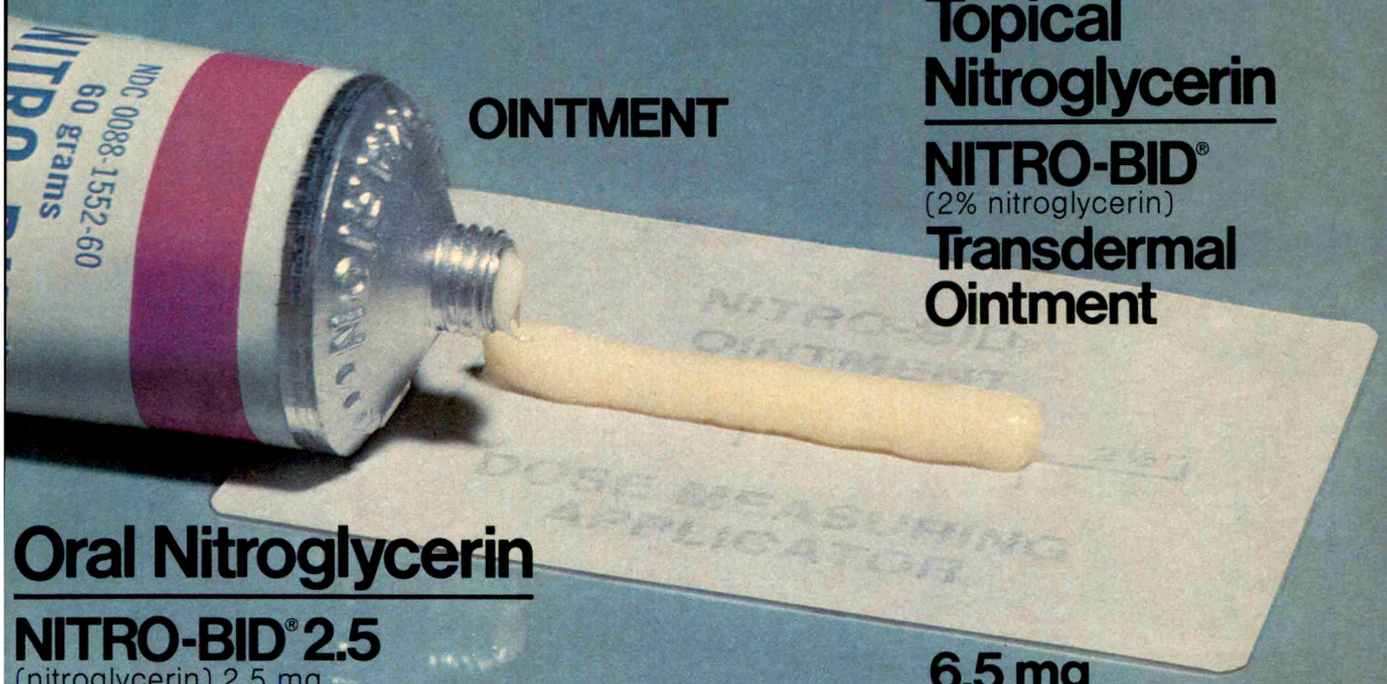
Of the greatest therapeutic importance is that type I antiarrhythmic (quinidine-like) agents appear to make the arrhythmia worse and may cause a disaster.[14] The management at present is (1) to correct the underlying cause, if recognized, (2) to use pharmacologic agents that shorten and equalize, not lengthen, the refractory period of cardiac muscle, and (3) to resort to electrical pacing, if required, with the realization that this also may make matters worse.[15]

Attention of a few clinicians to the morphologic features of standard electrocardiograms has disclosed one tachycardia of ventricular origin that not only can be produced by quinidine-like drugs but can have a fatal termination if treated with them. It seems likely that further investigation of the clinical aspects of ventricular tachycardias and fibrillation, including the details of their electrocardiographic configurations, will expand their classification and lead to more rational and effective clinical management.

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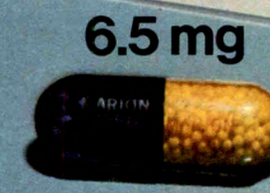
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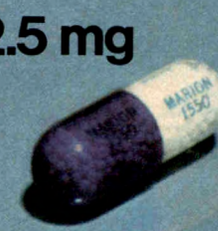
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"Possibly" effective. When applied topically, NITRO-BID Ointment is indicated for the prevention and treatment of angina pectoris attacks especially at night.

Final classification of the less-than-effective indications requires further evaluation.

Contraindications
Patients with marked anemia, increased intraocular pressure, increased intracranial pressure, glaucoma, hypotension, and idiosyncrasy to this drug.

Warnings
NITRO-BID is not intended to abort the acute anginal episode. NITRO-BID Capsules must be taken ORALLY, not sublingually. In terminating NITRO-BID Ointment treatment, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions.

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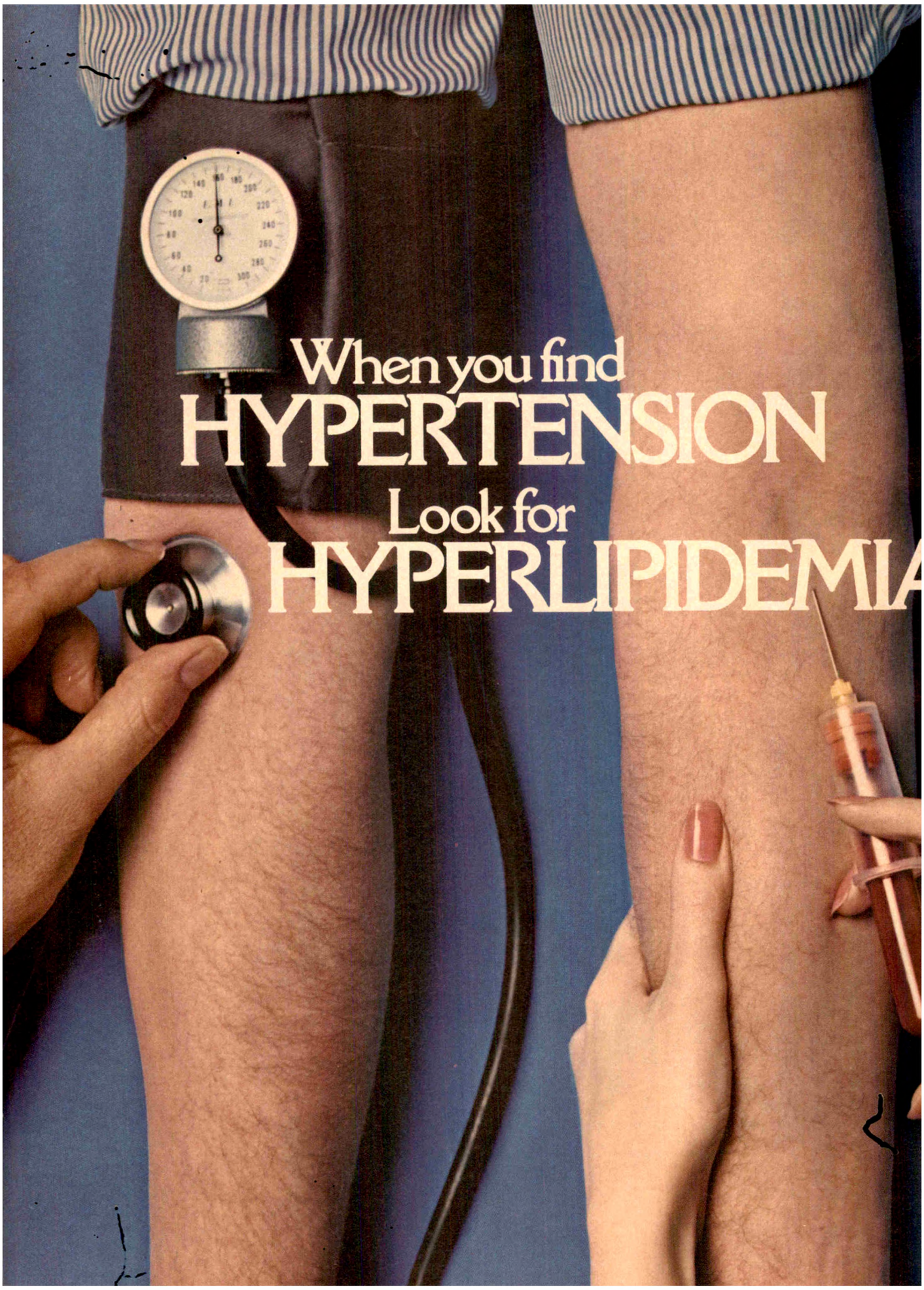
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Two out of every five hypertensives found to be hyperlipidemic in recent study[1]

Lipid abnormalities are often part of a broader clinical picture. For example, a recent study[1] reports an association between hypertension and hypertriglyceridemia—the most common form of hyperlipidemia. (See table below.)

Type of Hyperlipidemia*	Incidence of Hyperlipidemia	
	Hypertensives (89 subjects)	Normotensives (89 subjects)
Type IIA	9% (8)	7% (6)
Type IIB	6% (5)	3% (3)
Type IV	26% (23)	11% (10)
Total	**41% (36)**	**21% (19)**

*Hyperlipidemia was diagnosed when cholesterol levels exceeded 282 mg% and /or triglycerides were over 177 mg%—cutoff points higher than the usual upper limits of normal.
Adapted from Thomas, G. W., *et al.*[1]

The essential measurements—cholesterol *and* triglycerides

Today, lipid determinations are recommended as part of every general medical examination.

Because elevated lipids may coexist with high blood pressure, it is especially important to screen hypertensive patients for hyperlipidemia. Testing for both cholesterol *and* triglycerides is considered essential,[2-5] since it increases the chances of detection from 6 out of 10 to 9.5 out of 10.[6]

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

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significantly lowers serum levels of cholesterol and/or triglycerides

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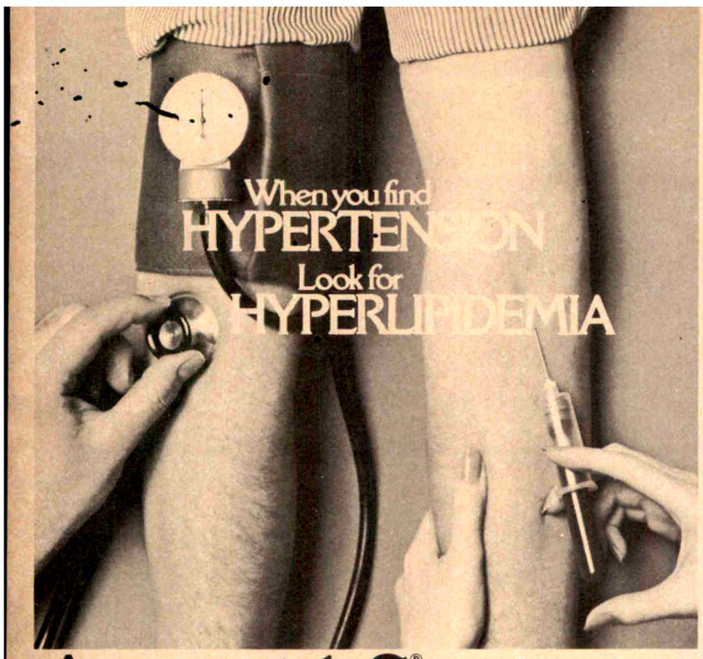
Patient acceptance is generally good

In more than a decade of use, clofibrate has been generally well tolerated. Major adverse effects are primarily gastrointestinal, with nausea being predominant. Other G.I. reactions include loose stools, flatulence, abdominal distress, and, infrequently, gallstones. Less common reactions include muscle cramping, myalgia, and alopecia. Please see "Important Note" at left and Warning on concomitant anticoagulant usage in prescribing information on following page.

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

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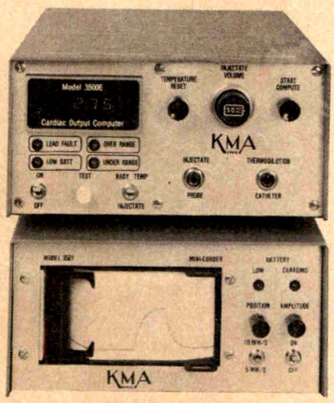
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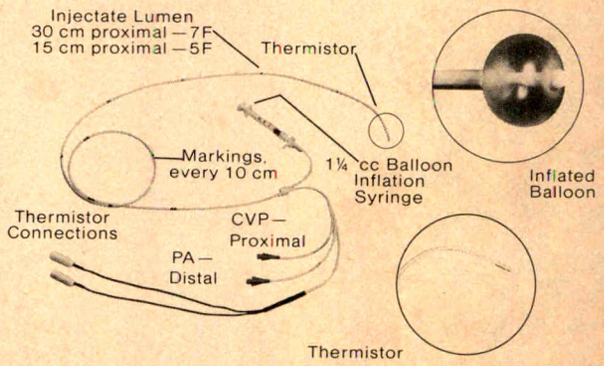
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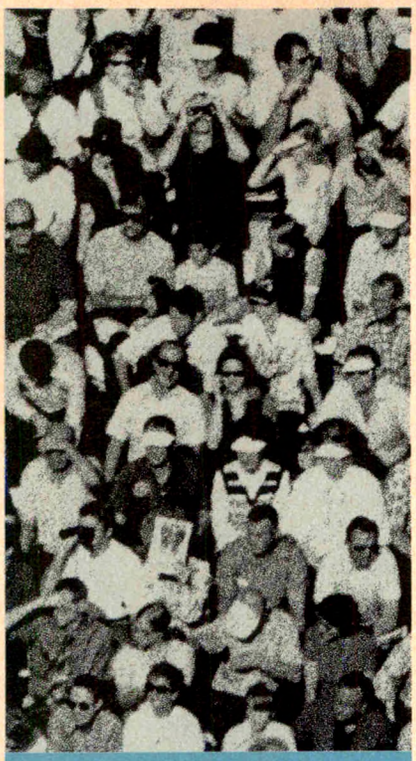


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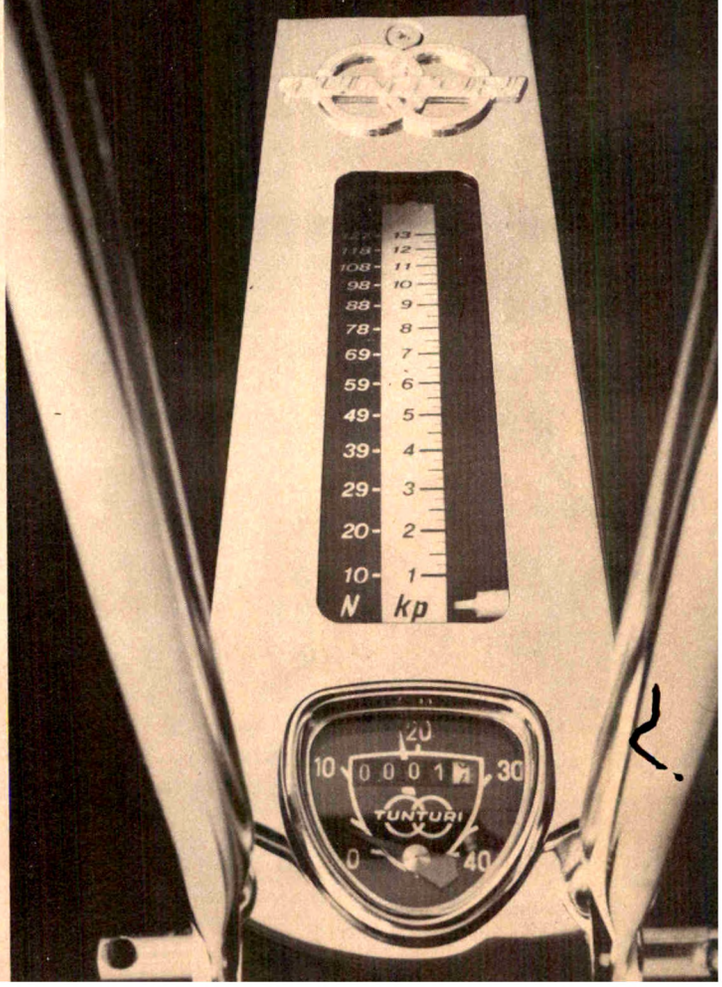
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LETTERS TO THE EDITOR

MIRANDA AND THE PATIENT WITH CORONARY DISEASE

The Supreme Court of the United States, in June of 1966, made a landmark decision in the case of Miranda vs. State of Arizona. The Court decreed that a criminal, on arrest or apprehension, shall be advised of his constitutional rights and that these shall include the right to silence and the right to counsel. The wisdom of this Court decision might be questioned by some but it remains the law of the land. If a lowly criminal has inalienable rights, why shouldn't the patient who suffers from coronary artery disease? He may not need counsel, but he certainly has the right to know what is available to him in the way of diagnosis and treatment.

Coronary arteriography for all?: The Sones technique of coronary arteriography was introduced in 1958. Although intended to be a diagnostic procedure, it opened a Pandora-like box that included modern revascularization surgery. The past two decades of clinical usage have shown this diagnostic adjunct to be invaluable in determining the precise needs of the patient with coronary artery disease. Some of us believe that coronary arteriography is essential for complete evaluation of the patient who is suspected of having coronary artery disease. Yet many cardiologists and internists use arteriography sporadically or not at all. Why some patients require a precise form of diagnosis, while the majority do not, puzzles many of us. The statement is often heard: "We cannot catheterize *everybody.*" Maybe not, but few of our good cardiovascular laboratories are taxed beyond their limits of productivity.

Before 1958 ischemic heart disease was considered a medical problem from the standpoint of both diagnosis and therapy. Contrary to the views of some cardiologists, this is no longer the case. When a patient is suspected of having coronary artery disease he should have the right to know that coronary arteriography may be available and helpful. We believe that this invasive technique is the sine qua non of diagnosis in coronary disease and should always be recommended unless a specific contraindication exists.

The doctor-patient relation: The traditional cardiologist often played a tyrannical role in the doctor-patient relation and assumed all prerogatives of decision-making. In the past this attitude was understandable, but tremendous strides have been made in the diagnosis and the treatment of coronary artery disease as times have changed. Coronary cinearteriography is more than 20 years of age, and modern revascularization surgery is now in its 11th year. Coronary arteriography is no longer an experimental procedure; nor is it an automatic precursor to surgical treatment. In professional hands the risk is negligible. We find it difficult to understand why many physicians do not avail themselves of coronary arteriography but impose long-term medical programs on patients who have not had the benefit of precise clinical diagnosis. Thus, without benefit of arteriographic evaluation, symptomatic patients are advised to invest in track shoes so that they may run away from their disease. Or, in the saddest situation of them all, the patient with normal coronary arteries is treated medically for a malady that does not exist. It will be a long time before our high regard for coronary arteriography is shared by most members of the profession, but the time is coming when the clinician will have to advise his patient that such a procedure exists and may offer distinct benefit.

The patient's right to know the options: During the pa two decades there have been dramatic social changes that ha inflicted side effects upon the practice of medicine. The su geon has become sensitive to regulations concerning informe consent. Patients are advised to seek a second opinion wh operative treatment is recommended. Malpractice suits a commonplace and these have boosted the cost of insuran to unprecedented levels. It is only a matter of time when the will be a landmark decision against a cardiologist based on t simple fact that his patient was not informed of options in t diagnosis and therapy of coronary artery disease. The pro able first plaintiff will be the family of a patient who sustain a myocardial infarction or died suddenly; the allegations w state that the patient did not know that coronary arteriogr phy was available to him and that he might have been a ca didate for revascularization surgery that could have be life-saving.

At this time it would seem that every patient with corona artery disease is entitled to know the options available to hi Disregarding the legal implications, surely the patient's rig to know constitutes a basic ethic. Every physician and eve surgeon is entitled to independent thought, but none of have the divine right to render an arbitrary decision when variety of diagnostic and therapeutic options are available

Donald B. Effler, MD, FACC
Goffredo G. Gensini, MD, FACC
St. Joseph's Hospital Health Cent
Syracuse, New York

ACUTE MYOCARDIAL INFARCTION WITH NORMAL CORONARY ARTERIES

With their most recent contribution to this Journal,[1] Oliv and colleagues are to be congratulated on their series of im portant observations that come as a result of their bold in vasive approach to patients with acute ischemic cardia pain.[2,3] It seems increasingly clear that coronary arteri spasm plays an important role in ischemic cardiac disease, we beyond its role in the relatively small subgroup of patien with Prinzmetal's variant angina in whom spasm has bee recognized as one pathogenetic mechanism. The complex ro involving the interaction of spasm and platelet aggregatio remains to be worked out more precisely. With this in min we are curious whether Oliva and Breckinridge made any a tempt to dilate the distal left anterior descending coronar arterial lesion they noted in their Case 2 with "normal or ne normal coronary arteries." [1]

On the basis of their recently reported experience with in tracoronary nitroglycerin,[3] such an attempt might have bee safely undertaken both to permit possible preservation myocardium (although the infarct was already almost 12 hou old and was certainly larger than one that would have bee caused by the lesion they described) and to help answer som of the questions they raise about possible causal mecha nisms.

With regard to these questions, it seems possible tha platelet aggregation is more likely be a secondary than a pr mary phenomenon, and we propose the following comple sequence of events as a possible explanation for what ma

occur: coronary arterial vasospasm (induced by any of a number of mechanisms) → endothelial cell damage[4,5] → platelet aggregation after exposure of platelets to vascular collagen,[6] platelet-induced release of a local vasodilator (for example, prostacyclin) from the endothelium[7,8] → reversal of the initial vasospasm → distal embolization of these platelets aggregates, leading to the exact conditions in the first and second infarction in their Case 2, namely, normal major coronary arteries with small distal occlusions shown after the initial event.

In addition to the administration of dipyridamole, as suggested by Oliva and Breckinridge, other platelet inhibitors, such as aspirin[9] or sulfinpyrazone,[10] might be reasonable alternatives, or even used with dipyridamole to achieve a maximal suppression of platelet activity in patients with coronary vasospasm.

Finally, we emphasize that patients with acute ischemic cardiac pain and acute myocardial infarction can safely undergo coronary angiography if handled with great care and skill. The use of this tool can be an extremely important adjunct to the therapy and understanding of what is happening in such patients. Whether infarcts can be reduced in size by therapy administered by such aggressive invasive techniques is not known. The answer must await the outcome of what we hope will be very carefully designed clinical investigations.

Richard C. Pasternak, MD
Roman W. DeSanctis, MD, FACC
Massachusetts General Hospital
Boston, Massachusetts

S. David Gertz, PhD
Department of Anatomy and Embryology
The Hebrew University
Hadassah Medical
Jerusalem, Israel

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10. The Anturane Reinfarction Trial Research Group: Sulfinpyrazone in the prevention of cardiac death after myocardial infarction. N Engl J Med 298:289–295, 1978

REPLY

No attempt was made to dilate the distal left anterior descending coronary artery in Case 2 with intracoronary nitroglycerin because the obstruction was not recognized in the catheterization laboratory in the video tape. This small distal obstruction and the similar distal obstruction in the posterior descending artery 2 weeks earlier were only recognized later in the cineangiogram.

We agree that the pathophysiology of acute myocardial infarction with or without underlying coronary artery disease is probably a complex sequence of events. In the presence of coronary artery disease the interaction of coronary arterial spasm, platelet aggregates and the atherosclerotic plaque may be fundamental. In the absence of coronary artery disease an interaction between coronary arterial spasm, platelet aggregates and endothelial cells may provide a comparable fundamental substrate. Substances such as prostacyclin, thromboxane A_2, potassium and catecholamines—which affect coronary reactivity and, in some instances, platelet aggregability—contribute to the complexity of the infarction process. The precise sequence of events in the pathophysiology of acute myocardial infarction is, of course, uncertain. Further carefully conducted studies in man during the early hours of the infarction process will be helpful.

Philip B. Oliva, MD, FACC
John C. Breckinridge, MD, FACC
Cardiology Division
Denver General Hospital
Denver, Colorado

ERGONOVINE MALEATE, ANGINA-LIKE SYNDROME AND CORONARY SPASM

In the recent article by Heupler et al.[1] on ergonovine maleate provocative tests for coronary arterial spasm, Table I states that group C (66 patients) had angina-like chest pain. However, only three patients in this group had typical angina; the remainder were considered to have atypical angina. In attempting to keep up with the literature, small shortcuts such as tables, charts and graphs are quite helpful, but we would like the editors and reviewers of articles to be quite sure that these tables and charts are accurate and not described differently under Methods, Results or Discussion.

To comment further, under the catheterization protocol the patients were given nitroglycerin anywhere between 15 and 45 minutes before the injection of ergonovine maleate. Because nitroglycerin may be effective for this period of time, I fail to understand how the protocol could be used when nitroglycerin is the therapy for ergonovine maleate spasm. We have no idea how many patients received the nitroglycerin at 15 minutes and how many at 45 minutes. Only 16 patients received 0.3 mg, which is not a large dose, and 50 patients, or a little more than 50 percent, did not receive a dose that may be appropriate to produce spasm. The authors therefore cannot rule out the possibility that larger doses in these patients with the angina-like syndrome might have produced coronary arterial spasm.

Joseph P. Liss, Jr., MD, FACC
Exercise Laboratory and
Section of Cardiac Rehabilitation
Saint Francis Hospital and Medical Center
Hartford, Connecticut

Reference

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REPLY

For patients in Group C, we used the term angina-like chest pain, instead of the term angina in order to include patients with typical as well as atypical angina. As we stated, this was a heterogeneous group of patients without severe coronary obstructions who had in common one clinical feature: a chest pain syndrome suggestive of angina pectoris. In practice, we

see patients with normal coronary arteriograms and a spectrum of chest pain syndromes, from very typical to very atypical angina. The term "angina-like chest pain" seems to me quite satisfactory to describe these patients. The same terminology has been used by other authors[1] to describe a similar group of patients.

Nitroglycerin was administered before the ergonovine test in order to exclude "catheter-induced" spasm occurring coincidentally after the administration of ergonovine. If this practice were to have any effect, it would be to decrease the sensitivity of the ergonovine test. We were willing to accept this in order to maintain the specificity of the test. However, in spite of this protocol, the test still had a remarkably high level of sensitivity. Also, our protocol matches the usual clinical situation. After performing routine coronary arteriography, during which vasodilators are given, the angiographer may then immediately perform the ergonovine test if no major coronary obstructions are demonstrated. He does not need to wait for the nitroglycerin effect to wear off. The length of time between the administration of nitroglycerin and the performance of the ergonovine test could not account for the differences in ergonovine response among the four groups of patients because the intervals were similar in each group.

I find no justification for the statement by Liss that 50 percent of the patients "did not receive a dose that may be appropriate to produce spasm." Our dose-response curves clearly demonstrate that 0.2 mg of ergonovine maleate appears to be the appropriate dose for producing severe coronary spasm in the majority of patients with Prinzmetal's variant angina and no fixed severe coronary obstructions. Similar doses of ergonovine maleate do not produce severe coronary spasm in the majority of other patients. All 98 patients in this study received at least 0.2 mg, unless 0.1 mg produced a positive test.

Frederick A. Heupler, Jr., MD
Cleveland Clinic
Cleveland, Ohio

Reference

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CARDIAC RUPTURE AFTER MYOCARDIAL INFARCTION

In the review on cardiac rupture by Bates et al.,[1] we note inaccuracies respecting our case report,[2] which was cited three times but with inadequate regard for the facts.

We reported on a 45 year old patient whose left ventricle ruptured 21 days after myocardial infarction; selective coronary angiograms and a left ventriculogram had been made 8 days earlier when infarctectomy was considered for control of serious ventricular arrhythmia. Ingravescent cardiorrhexis was suspected clinically and confirmed with pericardiocentesis and induction of pneumopericardium. During a long and difficult surgical procedure this gravely ill patient had a 40 g, 45 cm anterolateral myocardial infarct resected as well as coronary bypass vein grafting. He did extremely well and we reported angiocardiographic studies made 6 months and an exercise test made 1 year after operation. Seven years after his infarct, the patient remains completely well with normal exercise tolerance; he has no cardiac symptoms and is taking no medications except drugs influencing platelet behavior. He has a notably small cardiovascular silhouette.

Our paper[2] was the first to describe successful surgical treatment of postinfarction cardiac rupture. It was nine pages long, the case report was thoroughly documented clinically, surgically and pathologically, and the illustrations were good. We believe it was written in simple, easy to understand English. Consequently we are astonished by the three references to it in the review by Bates et al.[1]:

"The most common presentation is sudden unanticipated death although survival for up to 3 weeks after cardiac rupture has been reported." (p. 433)

"Surgical intervention in cases of cardiac rupture has remained, until recently, essentially speculative and the results have been poor." (p. 434)

"The long-term prognosis for patients surviving surgical repair of a ruptured ventricle may be excellent. For example, one patient . . . ; another patient, 1 year after surgery was participating in athletic activities including cross-country skiing." (p. 434, 24 lines below the last quotation).

Keeping 96 references in perspective must have been difficult for these review authors. Doubtless the other 95 have been dealt with quite faithfully.

Gerald M. FitzGibbon, FACC, FRCP(C)
G. David Hooper, MD, FRCS(C)
H. Alexander Heggtveit, FACC, FRCP(C

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REPLY

The first observation (on survival up to 3 weeks) refers t survival without surgery. The second observation (surgica management is essentially speculative and results are poor refers to the overall reported experience as well as to multipl unreported unsuccessful efforts that have been communicate to us. With reference to the third observation (results 1 yea after surgery), we point out that, at the time of the authors report, that was the extent of their follow-up! We received th information about their long-term follow-up as of 1978 wit great interest.

C. E. Anagnostopoulos, MD, FAC
Cardiac Surgery
Department of Surgery
The University of Chicago
Chicago, Illinois

PROGNOSIS IN SEVERE UNSTABLE ANGINA PECTORIS

Alison et al.[1] noted that the short-term prognosis in thei patients admitted to the hospital because of unstable angina pectoris was determined mainly by the underlying coronary arterial anatomy. However, they state that patients who sustained a myocardial infarction or died in the hospital had unstable angina that usually met the criteria of an extremely high risk subgroup of patients with "preinfarctional angina" described by Gazes et al.[2] or a subgroup with an "intermediate syndrome" described by Bertolasi et al.[3] These patients would probably fit nicely into what we refer to as the category of patients with the condition type II (severe) unstable angina. We agree that the severity of the coronary disease and the status of left ventricular function are the major determinants of prognosis, but we wonder whether the clinical presentation is not another determinant.

It would be of extreme interest to know how many patients in the total group of 188 satisfied the criteria for severity of angina cited and the percent of such patients, if any, with normal coronary arteriograms. Can the total number of patients studied be divided into those who met such criteria for severity and those who did not? It would be of value to find out if a statistically significant difference between the two subgroups may exist with regard to coronary arterial anatomy and the in-hospital morbidity and mortality.

Robert A. Chahine, MD, FACC
Robert J. Luchi, MD, FACC
Baylor College of Medicine
Veterans Administration Hospital
Houston, Texas

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REPLY

Unfortunately, the descriptions of chest pain were not sufficiently recorded to tell how many patients qualified for "severe unstable angina." However, in the patients sustaining a myocardial infarction or dying during hospitalization, the chest pain symptoms were adequately described and 75 percent (8 of 12) probably met the criteria for "severe unstable angina." This presumably reflected the tendency of physicians to maintain better records on their more seriously ill patients.

Chest pain symptoms in the total group were recorded adequately enough to form some conclusions about their prognostic significance. Among the various anatomic subgroups with the syndrome of unstable angina pectoris, the percent of patients from each group with chest pain at rest in the hospital were as follows: "normal" 70 percent (14 of 20), mild to moderate coronary artery disease 67 percent (8 of 12), left main coronary artery disease 83 percent (10 of 12) and severe coronary artery disease without left main involvement 91 percent (112 of 123). Of the patients sustaining a myocardial infarction or death, 82 percent (9 of 11) had angina at rest during their hospital course. These data indicate that for the individual patient with chest pain, pain at rest is a poor discriminator of the presence or absence of severe coronary artery disease.

An electrocardiogram taken during episodes of chest pain at rest was helpful in predicting abnormal coronary anatomy and was of some benefit in predicting risk of in-hospital myocardial infarction or death. Of the 123 patients who had an electrocardiogram taken during an episode of chest pain at rest, 89 (72 percent) had ischemic S-T segment changes (1 mm or more) indicating significant coronary disease. Of these 89 patients, 86 (96.6 percent) had 70 percent stenosis or greater of at least one major coronary artery, 2 (2.3 percent) had 50 percent stenosis of the coronary arteries and 1 (1.1 percent) had a normal coronary arteriogram. In those 12 patients sustaining a myocardial infarction or dying, 8 of 9 (89 percent) had ischemic S-T segment changes during episodes of angina at rest. Thus, 9 percent of patients (8 of 89) having an ischemic S-T segment response and 2.9 percent of patients (1 of 34) not having ischemic S-T segment changes during episodes of chest pain at rest subsequently died or had a myocardial infarction.

In summary, the clinical presentation in our series of patients with respect to ischemic S-T segment changes occurring at rest has important prognostic implications. Those patients having ischemic S-T segment changes almost always had severe coronary lesions and seemed to be at greater risk for in-hospital myocardial infarction or death.

Harold W. Alison, MD
Charles E. Rackley, MD, FACC
University of Alabama School of Medicine
Birmingham, Alabama

KUSSMAUL'S SIGN IN PERICARDIAL DISEASE

The report by Mann and colleagues[1] of effusive-constrictive pericarditis owing to neoplastic involvement of the pericardium is an excellent hemodynamic presentation of this subject and I am grateful to them for citing our original report.[2] They mention in passing (legend for Fig. 2) Kussmaul's sign, which persisted after pericardiocentesis. This important finding is of considerable diagnostic value. Many physicians (including cardiologists[3]) continue to believe that uncomplicated cardiac tamponade is accompanied by Kussmaul's sign, probably because of the difficulty of interpreting neck vein phenomena during rapid heart rates and labored breathing. In my experience, a verifiable Kussmaul's sign in the presence of pericardial effusion has invariably indicated some underlying additional restrictive involvement, usually by tumor or infiltration, of the epicardium or of the myocardium itself. Mann and colleagues have nicely demonstrated this in their valuable report.

David H. Spodick, MD, DSc, FACC
Department of Medicine
University of Massachusetts Medical School
and Division of Cardiology
St. Vincent Hospital
Worcester, Massachusetts

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2. **Spodick DH, Kumar S:** Subacute constrictive pericarditis with cardiac tamponade. Dis Chest 54:62, 1968
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REPLY

Previous reports provide a hemodynamic basis for Spodick's comments regarding the occurrence of Kussmaul's sign in pericardial disease. The right atrial pressure usually decreases with inspiration in patients with cardiac tamponade due to pericardial effusion; on the other hand, in patients with cardiac constriction or restriction, the right atrial pressure usually does not decrease with inspiration and in some cases may increase (the hemodynamic equivalent of Kussmaul's sign).[1–4] In the discussion section of our paper we mentioned that, before pericardiocentesis, failure of the right atrial pressure to decrease with inspiration may be a distinctive difference between acute tamponade due to simple effusion and subacute effusive constrictive pericarditis. This is an extremely subtle clinical finding and is probably best demonstrated by direct measurement of the right atrial pressure. However, the only

conclusive means of making the diagnosis of effusive constrictive disease is to demonstrate hemodynamic evidence of constriction after complete removal of the pericardial effusion.

Tift Mann, MD
Cardiac Catheterization Laboratory
Wake Medical Center
Raleigh, North Carolina

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APPLICATION SITE FOR NITROGLYCERIN OINTMENT

I read with interest the letter and reply on "Standardized Regimen for Applying Nitroglycerin Ointment." During my graduate work, I did a study[2] to determine the relative effectiveness of nitroglycerin ointment according to site of administration. To my knowledge, no studies of this type have been reported, and the findings may be useful.

The onset, magnitude and duration of effect of nitroglycerin ointment when the site of administration is varied was studied in 10 normal subjects ranging in age from 25 to 35 years. Systolic blood pressure, heart rate and pressure-rate product were used as measures of hemodynamic response. The application sites selected were: forehead, left lower anterior chest and the medial surface of the ankle. A control site (C) was selected randomly from the chest and ankle sites. Subjects were tested on 4 days for a period of 3 hours after baseline values were determined. A decrease of 10 mm Hg in systolic blood pressure was used to determine the effectiveness of the application.

Two-way analysis of variance showed significant differences among treatment sites and in the tendency for the treatments to show patterns over time ($P < 0.005$). A therapeutic effect, defined as a 10 mm Hg or greater decrease in systolic blood pressure, occurred in eight subjects with the forehead site, two with the ankle site and none with the control site. The mean duration of therapeutic effect was greater than 111 minutes with the forehead site, greater than 66 minutes with the chest site and greater than 32 minutes with the ankle site. A 10 beat/min increase in heart rate occurred in seven subjects and one subject, respectively, with the forehead and chest sites and in no subjects with the ankle or control site. Pressure-rate product determinations varied among subjects and treatment sites. Pressure-rate product tended to decrease with decreases in systolic blood pressure, although decreases, increases and fluctuations around the mean baseline pressure rate product occurred without therapeutic decreases in systolic blood pressure. There was a slightly greater incidence in number and severity of headaches associated with the forehead site. Six subjects with the forehead site reported headaches and five with the ankle and control sites had headaches. These data indicate hemodynamic variation according to topical administration of nitroglycerin ointment in normal subjects.

Mary Sue Hansen, RN, MA
Department of Physiologic Nursing
University of Washington
Seattle, Washington

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2. **Hansen MS:** Relative Effectiveness of Nitroglycerin Ointment According to Site of Ap plication: Hemodynamic Responses of Normal Subjects. Unpublished Master's Thesis University of Washington, Seattle, 1977

REPLY

Hansen's suggestion is of interest and importance, and ther are some experimental data in the rat to support it (H. I Fung, personal communication). However, the absence c specific information regarding the size of the surface area usec whether or not it was uniform and the dose employed pre cludes adequate evaluation of the information.

As indicated in our previous letter, measurement of plasm levels of nitroglycerin should permit a more systematic anal ysis of the optimal site and surface area over which nitrc glycerin can be absorbed. Such studies are now in progress

Paul W. Armstrong, MD, FACC
Department of Medicine (Cardiology)
Queen's University
Kingston, Ontario, Canada

COMMENT

Briefly, the dosage of nitroglycerin ointment was determine for each individual subject to find the lowest dose that woul produce a 10 mm Hg decrease in systolic blood pressure withi 1 hour. The amount of nitroglycerin used ranged from 0.5 t 2.0 inches (7.5 to 30 mg or 0.05 to 0.27 mg per pound of bod weight) and was placed in a 12 to 16 square inch area. (Th forehead sites were the smaller areas.) The ointment was no rubbed in and was covered with plastic wrap that was tape in place.

As Armstrong suggests, plasma levels of nitroglycerin wi certainly provide more quantitative data for study, and it wi be interesting to read of these further studies.

Mary Sue Hansen, RN, M

TECHNIQUE FOR CONTINUOUS ELECTRICAL PACING DURING PULSE GENERATOR REPLACEMENT

During unipolar pulse generator replacement, a pacemaker dependent patient may have cessation of cardiac action at th time of lead disconnection. Symptoms of cerebral insufficienc associated with this induced asystole are restlessness, ex pressive aphasia and convulsive movements. Although not a patients exhibit these symptoms, this potential complicatio can be avoided by using the following technique for continuou electrical pacing.

After exposing the pulse generator and electrode, insert 25 gauge needle into the negative lead wire a few inches fror the generator. To the shaft of this needle attach the negativ electrode from an external pacemaker; the positive lead fror this pacing device is connected to subcutaneous tissue aroun the wound. This now forms a loop bypassing the implante generator. Disconnect the negative electrode from the ol pulse generator and take threshold measurements. The connect the new generator to the negative lead and secure th set screw. The external pacemaker may now be disconnected the needle removed from the wire, and the small amount o surgical adhesive placed in the needle hole to keep body fluid out.

We have used this procedure in 50 patients with excellent results; it adds a definite safety factor to pulse generator replacement.

Ilhan Bahadir, MD
Ravi Koopot, MD, FACC
Edward B. Diethrich, MD, FACC
Arizona Heart Institute
Phoenix, Arizona

COMMENT

The technique described is an old one, and there are simpler ways to handle this problem without putting a needle through the insulation. The explanted pacemaker can be kept in contact with the tissues by using a battery clip (previously described)[1] to keep the circuit closed while the pacemaker wound is open and the pulse generator inspected. The anode of the external pacemaker is hooked to the battery clip, which is in turn grounded to the wound by a plate that has approximately the same surface area as the pulse generator. Disconnecting the cathode from the connector is a simple, rapid procedure and, once disconnected, the electrode can be attached to the other wire of the external pacemaker (the cathode), which will then be used for temporary pacing. In implanting the new pulse generator the process is reversed, first by placing the new pulse generator into the battery clip, and then quickly disconnecting the cathode from the external pacemaker and inserting it into its receptacle in the new pulse generator. Connecting and disconnecting the active external wire take no more than a few seconds.

It is a dangerous and unnecessary step to put a needle through the insulation of some of the modern wires, particularly the tinsel wires, because damage to the wire itself may occur. The needle will tear the insulation and, despite use of surgical cement, this area may act as a weak point for further insulation or wire fracture. Because this step is not needed, why do it?

Victor Parsonnet, MD, FACC
Department of Surgery
Newark Beth Israel Medical Center
Newark, New Jersey

Reference

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REBUTTAL

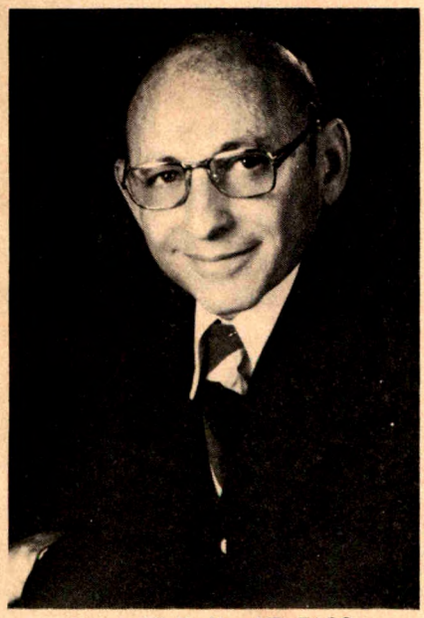
Parsonnet's technique does not afford any protection to the patient during disconnection of the cathode. In the normal situation, disconnecting the cathode is a simple and rapid procedure, and insertion of a needle into a lead wire is often not the most advisable method. But, in our practice during the past several years, we have encountered instances in which considerable difficulty arose during disconnection of the cathode (fracture of the cathode electrode, electrical discontinuity at the point of lead splicing or during adaptation to a different manufacturer's devices) producing electrical interruption and subsequent cardiac standstill.

We perhaps failed to make clear in our original letter that this technique is an emergency backup procedure for cases in which trouble arises during generator replacement in a pacemaker-dependent patient. It is not a routine technique but a valuable auxillary method should difficulty be encountered.

Ilhar Bahadir, MD
Ravi Koopot, MD
Edward B. Diethrich, MD

President's Page:

Implementation of American College of Cardiology Goals



Leonard S. Dreifus, MD, FACC

Among the recently adopted goals of the College are three that are receiving major attention at this time by your officers, boards and committees. These are: (1) to take an active role, in cooperation with appropriate organizations or agencies, in establishing standards for quality cardiovascular health care delivery and the review mechanisms necessary for periodic updating; (2) to function as a principal source of advice to government at all levels concerning cardiovascular health care delivery; and (3) to maintain a high level of social consciousness, concern for and involvement in the socio-economic aspects of cardiovascular health care delivery in the interest of providers, consumers and the public in general.

Addressing these three goals has embraced a major segment of the College's time and resources. Although many of the members have requested a detailed resumé, only a short summary of the College's activities can be described in this communication.

ICHD

I am pleased to report that the work of the Inter-Society Commission for Heart Disease Resources will be reactivated shortly under the leadership of Dr. Leonard Scherlis. All previous ICHD reports relative to criteria for quality cardiovascular health care will be reviewed and updated where necessary. Some new reports may need to be developed. The major sponsors of the ICHD activity are the American Heart Association and the American College of Cardiology.

Reimbursement Procedures in Teaching Hospitals

The College is particularly concerned that the Health Care Finance Administration might try to change the reimbursement procedures under Section 227 of P.L. 92-603. Implementation of this section would have an adverse effect on the finances of teaching hospitals and institutions. The Government Relations Committee of the College has moved this matter to top priority among our legislative concerns. Section 227 of this public law was enacted on October 30, 1972 but was never implemented because of various legislative maneuvers and amendments that extended Section 15 of P.L. 93-233 to October 1, 1978. However, upon its lapse, Section 227 would become law and drastically change the Medicare reimbursement basis for physicians located in teaching hospitals. It is our desire to work for the repeal of this section. We are currently using selected members of our Board of Governors to contact key legislators about this issue, and I was advised today that our concern and the concerns expressed by many others have led to an agreement by Secretary Califano of the Department of Health, Education, and Welfare to postpone for 1 year the implementation of Section 227.

Regulation of Medical Devices

Of great concern to our Governmen Relations Committee are the propose final regulations regarding medical de vices. The procedure for an investiga tional device exemption was published i the Federal Register in May 1978 (21 CFR part 1620 and 812). The College consid ers that Congress intended that the agency's first priority in implementing thi act was to encourage the discovery an development of useful medical devices However, the College sincerely believe that the Food and Drug Administration ha misread the intent of Congress and ha promulgated regulations that will shackl and discourage the investigation and de velopment of safe and effective medica devices. The very volume of these regu lations will deter teams of medical pro fessionals and manufacturers fron seeking advances in medical devices.

In addition, there will be little opportu nity to develop custom devices unde these new regulations. We believe that i was never the intent of Congress to hav a federal regulatory agency impose suc restrictions. The implementation of thes regulations will certainly directly affect th health and welfare of our patients.

Reimbursement for Echocardiograph

Recently, a combined representatio of our Government Relations and Car diovascular Procedures Committees me at Heart House with Dr. Roger O. Egeberg Chief Medical Officer, Bureau of Med care, DHEW, to discuss the Medicar reimbursement policy relative to echo cardiography. The College has maintaine that reimbursement of cardiologist should be equal to that of radiologists. W were successful several years ago i bringing about this equality. Now we fin that the radiologists have been quietly a work to change the reimbursement polic to one that would permit them to charg

20 percent more than the cardiologists for the same procedure. Their motivation is obvious, and we will vigorously oppose this discrimination since more than 90 percent of echocardiography is performed by cardiologists.

Determination of Disability

The College was invited to comment on the revised medical criteria for the determination of disability, as published in the Federal Register of July 12, 1978, and has effectively done so.

Other Issues

We were also invited to address the issues of outpatient cardiac catheterization, proposed regulations on research involving children, reimbursement policy for professional services as well as the criteria and standardization of free-standing cardiac rehabilitation units, and standards for cardiac monitors, heart rate meters and alarms. The College participated in an HEW-sponsored national conference to establish research planning principles as a prelude to the drafting of a comprehensive multi-year health research plan for our nation. And finally, the College submitted comments on House and Senate measures that called for the creation of a National Center for Health Care Technology.

It is quite apparent that the cross-disciplinary nature of cardiology embraces almost every facet of the health care delivery system. It appears that the American College of Cardiology will become even more actively involved in government legislation and regulation in the years ahead. The effective efforts of our Governors and many of the College membership in contacting appropriate members of Congress and other regulatory agencies have been extremely important in bringing into sharp focus the opinion of the American College of Cardiology. Happily, many of the final decisions and regulations emerge as the well reasoned opinions of the College.

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning, Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

DECEMBER 1978 THROUGH FEBRUARY 1979

Month/Dates	Course Director	Title of Program
1978		
December 4–6	Borys Surawicz, MD, FACC	**Advanced Cardiac Electrophysiology and Electrocardiography**
December 11–13	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**
1979		
January 24–26	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**
January 29–31	William C. Roberts, MD, FACC	**Congenital Heart Disease: The Multi-disciplinary Approach**
February 7–9	Robert S. Eliot, MD, FACC	**Coronary Artery Disease: Angina and Myocardial Infarction**
February 15–17	J. Willis Hurst, MD, FACC	**Controversies About Coronary Heart Disease and Its Treatment**
February 19–21	Sylvan L. Weinberg, MD, FACC	**CCU Update for Nursing Supervisors**

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

DECEMBER 1978 THROUGH FEBRUARY 1979

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

DEC 2–4 — **Advances in Heart Disease 1979.** Dean T. Mason, FACC, director, Fairmont Hotel, San Francisco, CA

DEC. 3–6 — **Coronary, Hypertensive, Valvular and Myocardial Heart Diseases: The Multidisciplinary Approach.** William C. Roberts, FACC, director, The Williamsburg Conference Center, Williamsburg Lodge, Williamsburg, VA

DEC. 8–10 — **Eleventh Annual Cardiovascular Symposium: Patient Oriented Management of Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, NY

DEC. 11–14 — **Core Curriculum: Interpretation and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, directors. Philadelphia Marriott Motor Hotel, Philadelphia, PA

1979

JAN. 15–19 — **Tenth Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Robert F. Grover, FACC and Bruce C. Paton, FACC, co-directors. Snowmass Resort, Snowmass, CO

FEB. 2–4 — **New Concepts in Clinical Electrocardiography.** William J. Mandel, FACC, and H. J. C. Swan, FACC, directors. Beverly Hilton Hotel, Los Angeles, CA

FEB. 14–16 — **Cardiovascular Disease—1979: Advances in Diagnosis and Management.** Kirk L. Peterson, FACC, John Ross, Jr., FACC, Ralph Shabetai, FACC, Allen D. Johnson, FACC and Gabriel Gregoratos, FACC, directors. Sheraton Harbor Island Hotel, San Diego, CA

AMERICAN COLLEGE OF CARDIOLOGY

Announces . . .

AFFILIATE IN TRAINING MEMBERSHIP

For Physicians in Cardiovascular Related Training Programs

Candidates for this membership category must be current full-time trainees in a recognized cardiovascular (adult, pediatric, surgical) related program in fulfillment of requirements for admission to a subspecialty board examination which holds membership in the American Board of Medical Specialties. Upon completion of training and in order to maintain an affiliation with the College, the members are encouraged to apply to the Credentials Committee for status in one of the other three membership categories.

The application for Affiliate in Training must be signed by the Director of the applicant's training program and two sponsors, both of whom must be Fellows of the College. One of the sponsors may be the Director of the training program, provided he is a Fellow of the College. The annual dues for an Affiliate in Training are $25.00.

Advantages to the Affiliate in Training

1. Subscription to *The American Journal of Cardiology,* the official journal of the College.
2. Reduced fees for all educational programs of the College.
3. Preference for enrollment in programs sponsored by the College with a limited registration.
4. Receipt of the quarterly publication, *Cardiology,* the newsletter of the College.
5. Participation in all affairs of the College as a member rather than as a guest of the College.

Those desiring an application form should write to Ms. Margaret E. Coffey, Director, Membership Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

28th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Miami Beach, Florida **March 11–15, 1979**

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Advances in Heart Disease, by Dean T. Mason, MD. New York, San Francisco, London, Grune & Stratton, 1978, 552 pages, $36.50

Cardiac Pathology, by Colin M. Bloor, MD. Philadelphia, Toronto, J.B. Lippincott, 1978, 430 pages

Circulatory Disease of the Limbs: A Primer, by David I. Abramson, MD. New York, Grune & Stratton, 1978, 367 pages, $19.00

Clinical Echocardiography, by Navin C. Nanda, MD and Raymond Gramiak, MD. St. Louis, Missouri, C.V. Mosby, 1978, 451 pages, $37.50

Clinical Nephrology, second edition, by Solomon Papper, MD. Boston, Little, Brown, 1978, 633 pages, $22.50

Comprehensive Immunology, The Immunopathology of Lymphoreticular Neoplasms, edited by J. J. Twomey, MB, Robert A. Good, MD and Stacey B. Day. New York, London, Plenum Medical Book, 1978, 763 pages, $45.00

Coronary Heart Disease in Young Women, edited by M. F. Oliver, MD. Edinburgh, London, New York, Churchill Livingstone, 1978, 262 pages, $23.50

Epidemiology of Diabetes and Its Vascular Lesions, by Kelly M. West, MD. New York, Elsevier North-Holland, 1978, 579 pages, $49.50

Essentials of Pediatric Cardiology, by James H. Moller, MD. Philadelphia, F.A. Davis, 1978, 202 pages, $9.95

Exercise and the Heart, edited by Nanette K. Wenger, MD and Albert N. Brest, MD. Philadelphia, F.A. Davis, 1978, 246 pages, $35.00

Hazards of Medication, by Eric W. Martin, PhD. Philadelphia, Toronto, J.B. Lippincott, 1978, 686 pages, $39.50

ISAM 1977. Proceedings of the Second International Symposium On Ambulatory Monitoring, by F. D. Stott, E. B. Raftery, P. Sleight and L. Goulding. London, New York, San Francisco, Academic Press, 1978, 331 pages, $21.75

Mechanisms of Vasodilatation, by Paul M. Vanhoutte and I. Leusen. Basel, Munchen, Paris, London, New York, Sydney, S. Karger, 1978, 307 pages, $53.50

The Metabolic Management of the Critically Ill, by Douglas W. Wilmore, MD. New York, London, Plenum Medical Book, 197
262 pages, $22.50

MGH Textbook of Emergency Medicine, by Earle W. Wilkin
Jr., MD, James J. Dineen, MD, Ashby C. Moncure, MD ar
Catherine P. Fitzgerald, BA. Baltimore, Maryland, Williams
Wilkins, 1978, 829 pages

**Modern Electrocardiology, Proceedings of the IVth Internation
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September 1977,** edited by Z. Antaloczy, MD. Amsterdan
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G. Anido, MD, M. Divernois-Merz, H. Drescher, MD, E. J. va
Kampen, PhD. Bern, Stuttgart, Vienna, Hans Huber Publisher
1978, 142 pages

Noninvasive Diagnostic Techniques in Vascular Disease, b
Eugene F. Bernstein, MD. St. Louis, Missouri, C.V. Mosby, 197
437 pages, $42.50

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York, Chichester, Brisbane, Toronto, John Wiley & Sons, 197
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Progress in Hemostasis and Thrombosis, Vol 4, edited b
Theodore H. Spaet, MD. New York, San Francisco, Londo
Grune & Stratton, 1978, 410 pages, $34.50

Regulation of the Capacitance Vessels, by A. M. Chernukh,
I. Tkatchenko, A. G. B. Kovach and S. Biro. Budapest, Akademi
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perimental Medicine and Biology,** Vol 102, edited by H. Jame
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The American Journal of CARDIOLOGY®

VOLUME 42
JULY TO DECEMBER
1978

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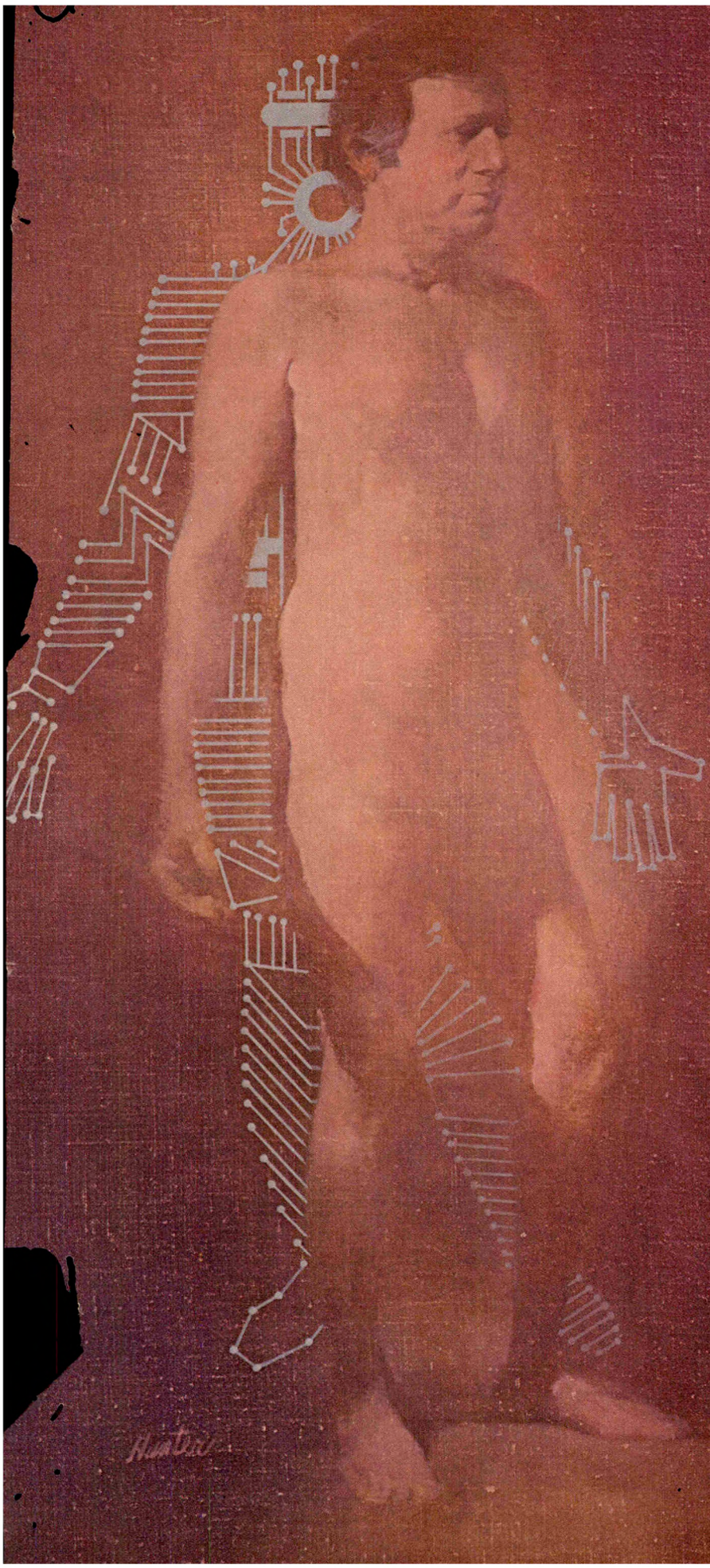
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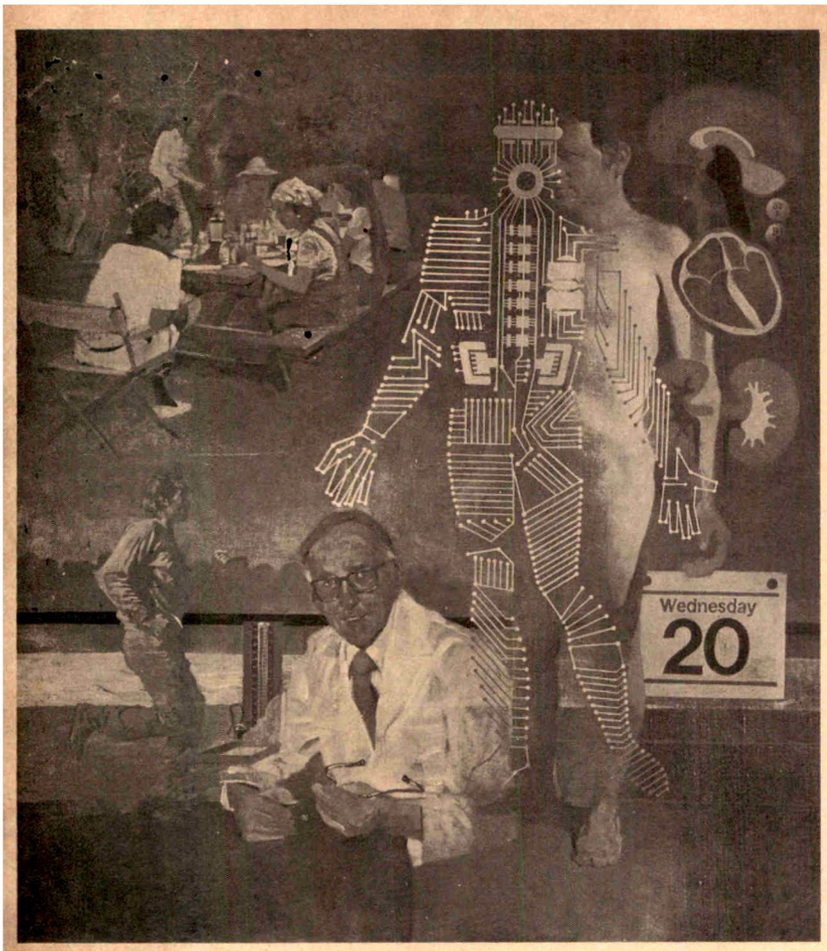
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Please see brief summary of prescribing information on last page of advertisement for warnings, precautions, and adverse reactions.

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1. Wilber JA, Barrow JS: Am J Med, 52:653-663, 1972.
2. Data on file at Boehringer Ingelheim Ltd.

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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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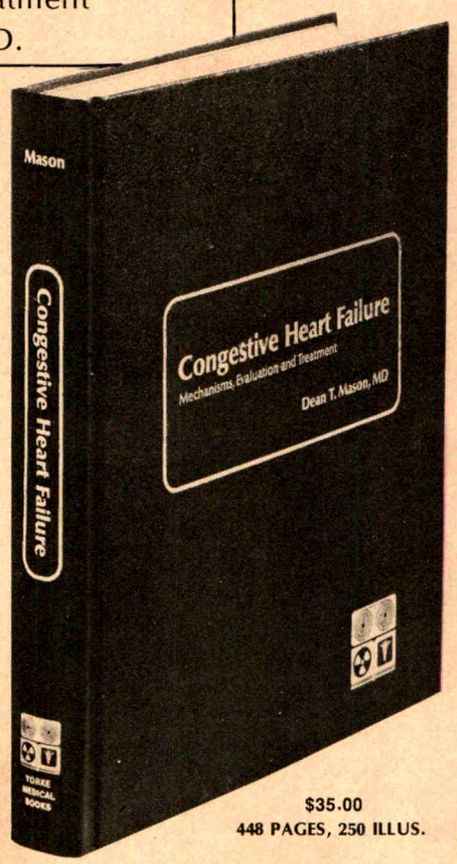
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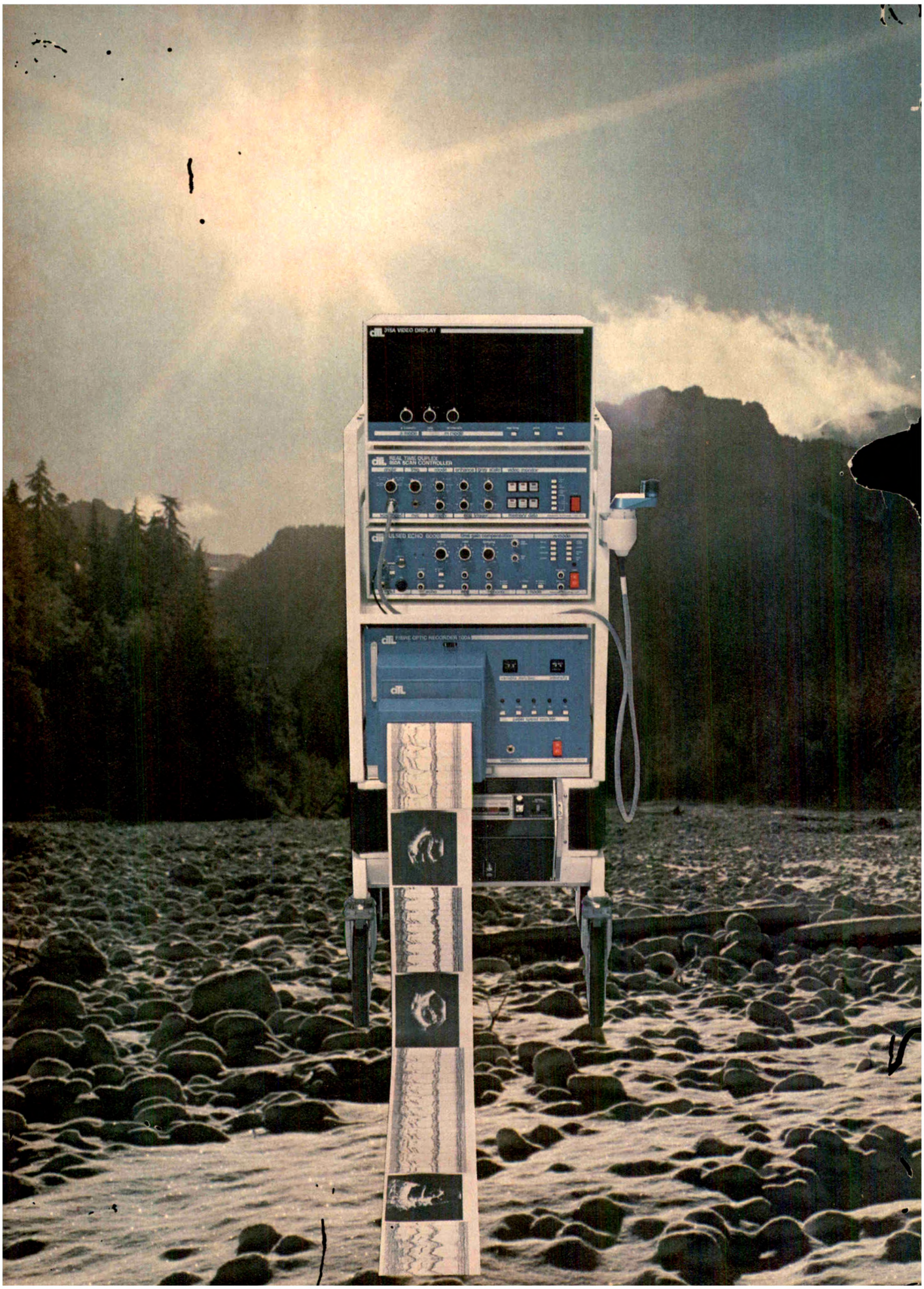
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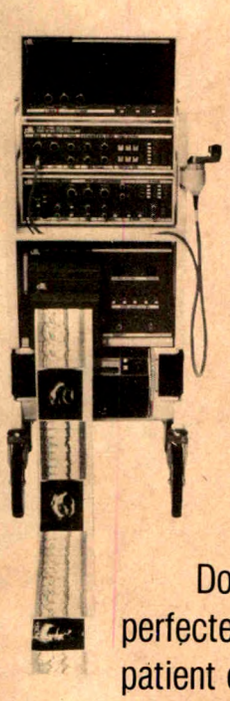
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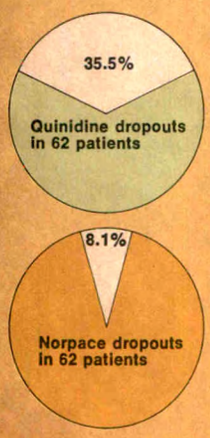
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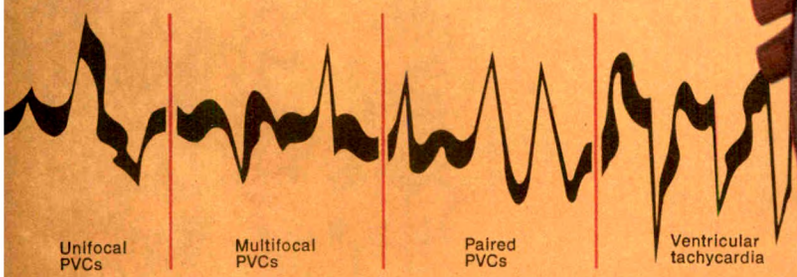
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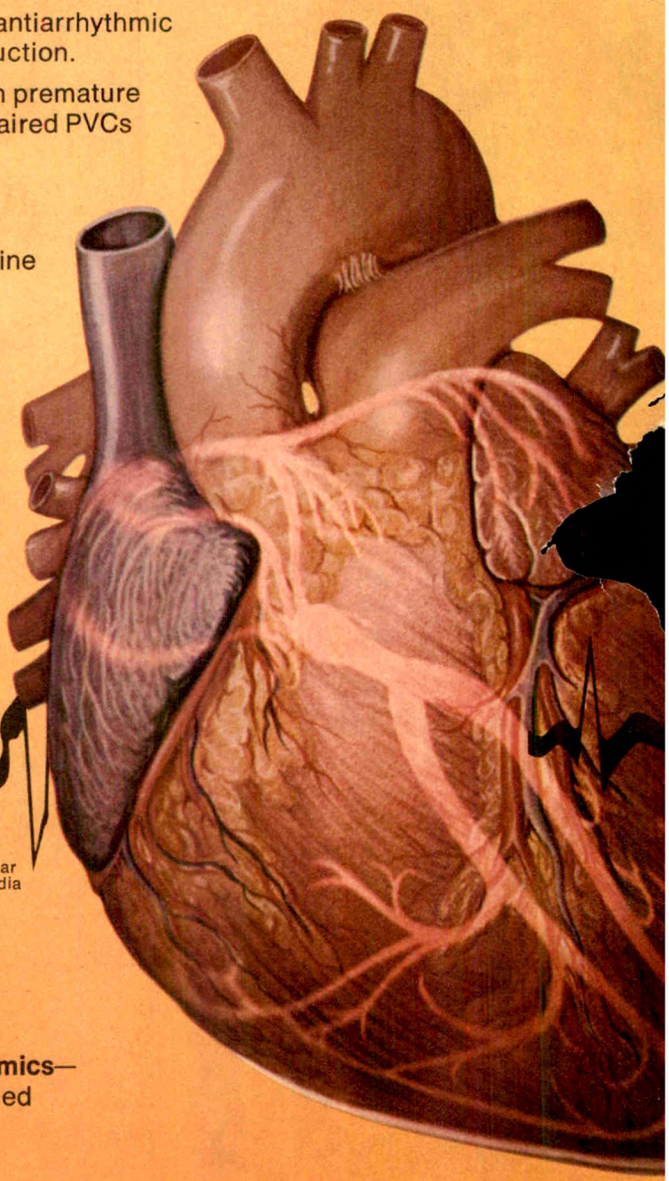
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Dose-related plasma levels—Plasma levels correlate closely with dosage.

Norpace (disopyramide phosphate) effect on hemodynamics—Rarely alters blood pressure significantly at recommended doses. May reduce cardiac output by about 10%.

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:
Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.
Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.
Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished.

In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained with appropriate treatment. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction, evidenced by widening of the QRS complex and/or prolongation of the Q-T interval.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.
Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

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Dosage and administration—Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily.

Initial Norpace dosage

Patients 110 lb or more	150 mg q 6 h
Patients less than 110 lb	100 mg q 6 h
Patients with specific complications: Patients with *possible cardiac decompensation, cardiomyopathy, reduced left ventricular function* or *hypotension* due to these or other causes	100 mg q 6 h
Patients with moderate renal impairment ($C_{Cr} > 40$ ml/min) or hepatic insufficiency	100 mg q 6 h (200-mg loading dose optional)
Patients with severe renal insufficiency ($C_{Cr} < 40$ ml/min)	100 mg given approximately every half-life ($T_{1/2}$) (200-mg loading dose optional)
C_{Cr} = 40–15 ml/min	q 10 h
C_{Cr} = 15– 5 ml/min	q 20 h
C_{Cr} = 5– 1 ml/min	q 30 h
In patients *without the complications* specified above in whom rapid control of arrhythmias is essential, therapy may be initiated with a loading dose of 300 mg (200 mg for patients under 110 lb).	

For complete Norpace dosage recommendations, please see complete prescribing information, a brief summary of which appears below.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy. *Use in Pregnancy and Lactation:* Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, hypoglycemia, (usually in patients with impaired liver function), and dysuria. Acute psychosis and cholestatic jaundice, both reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

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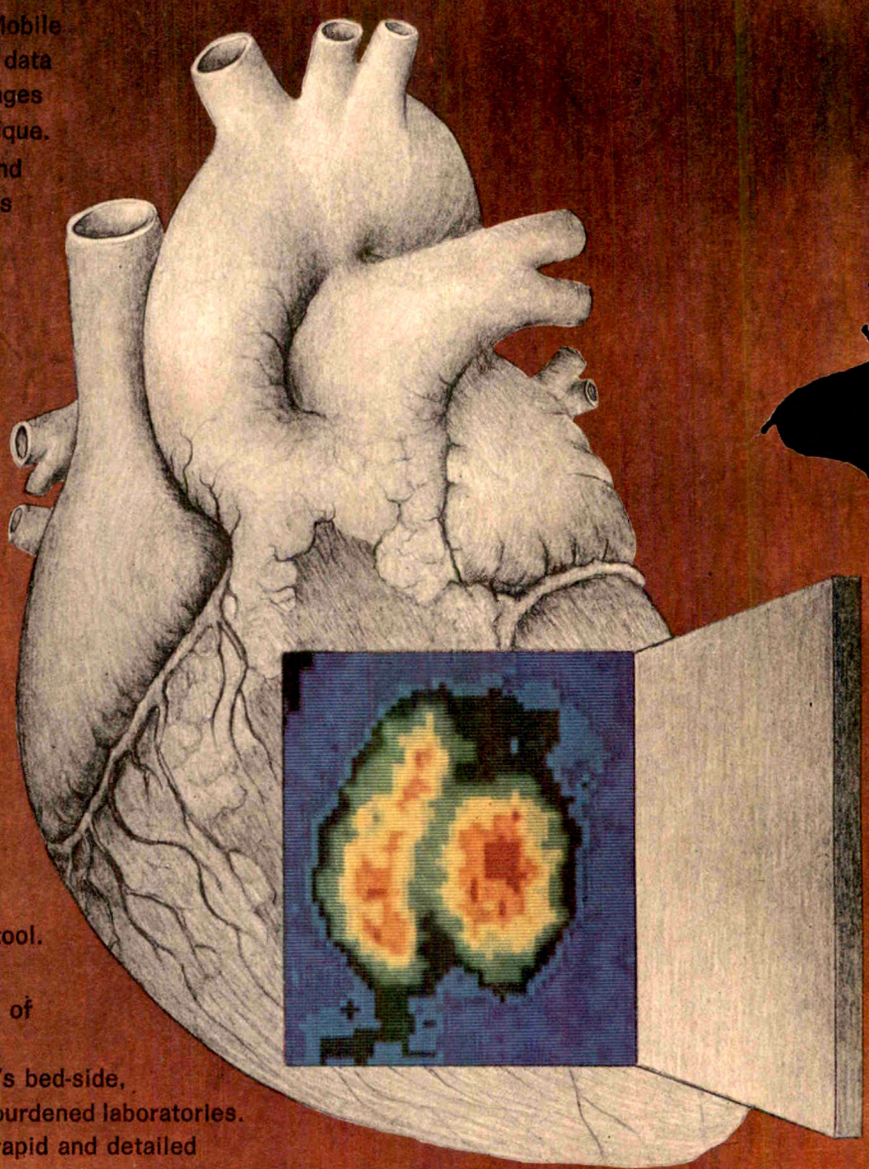
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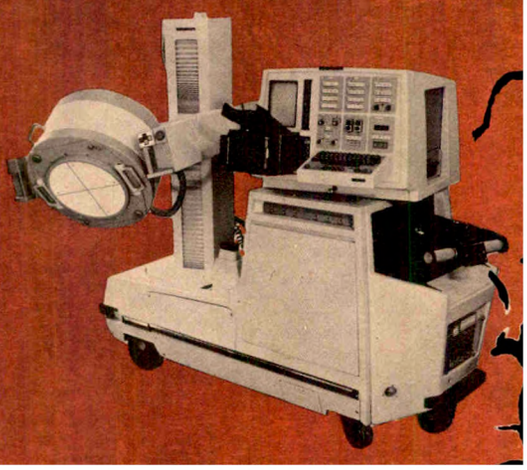
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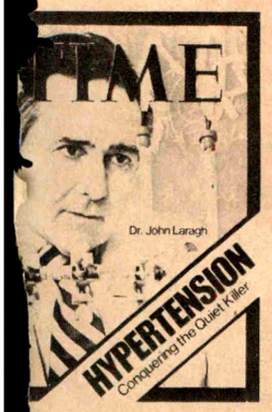
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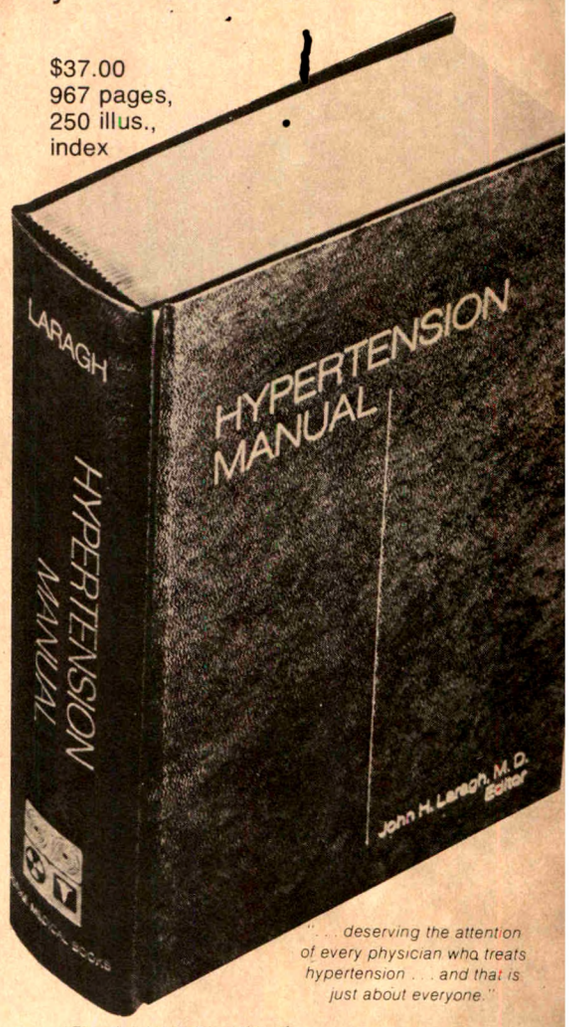


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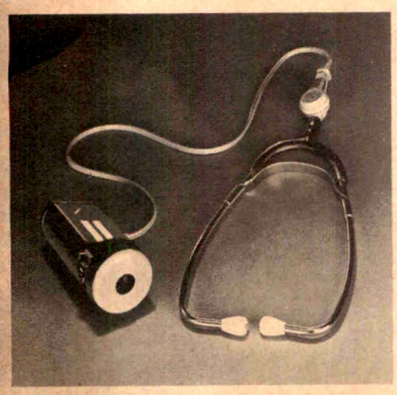
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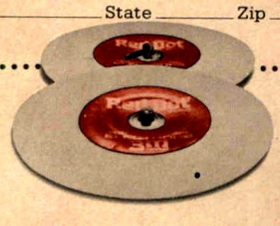
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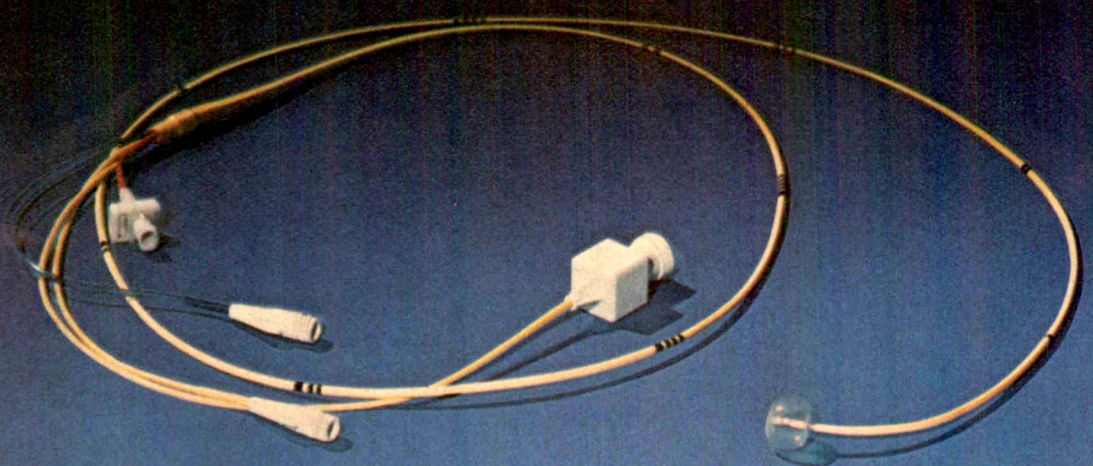
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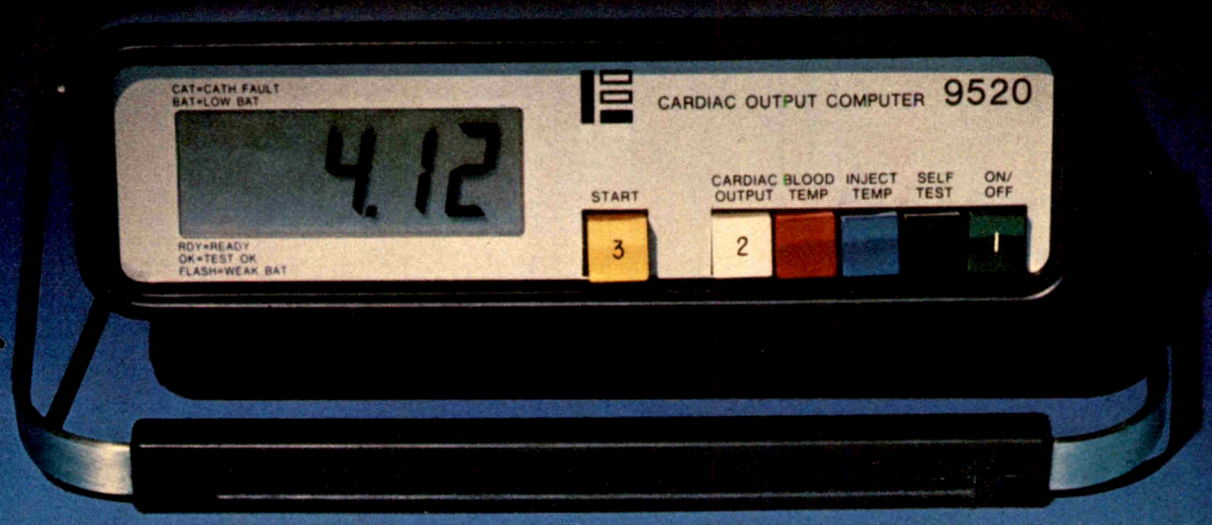
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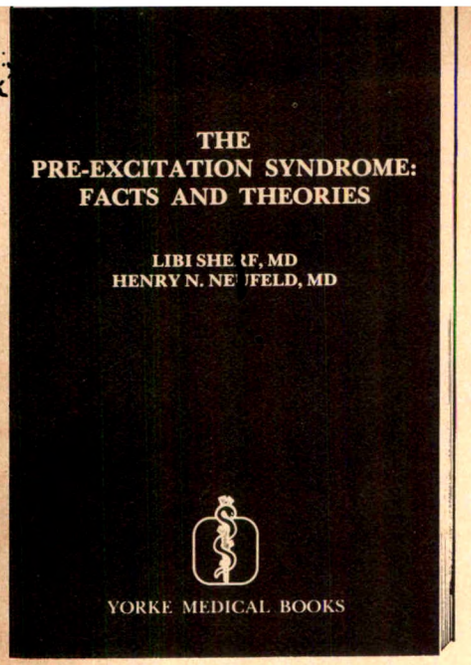
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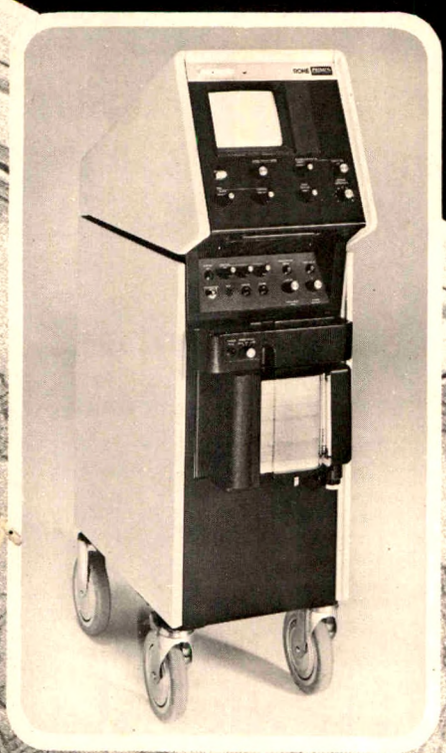
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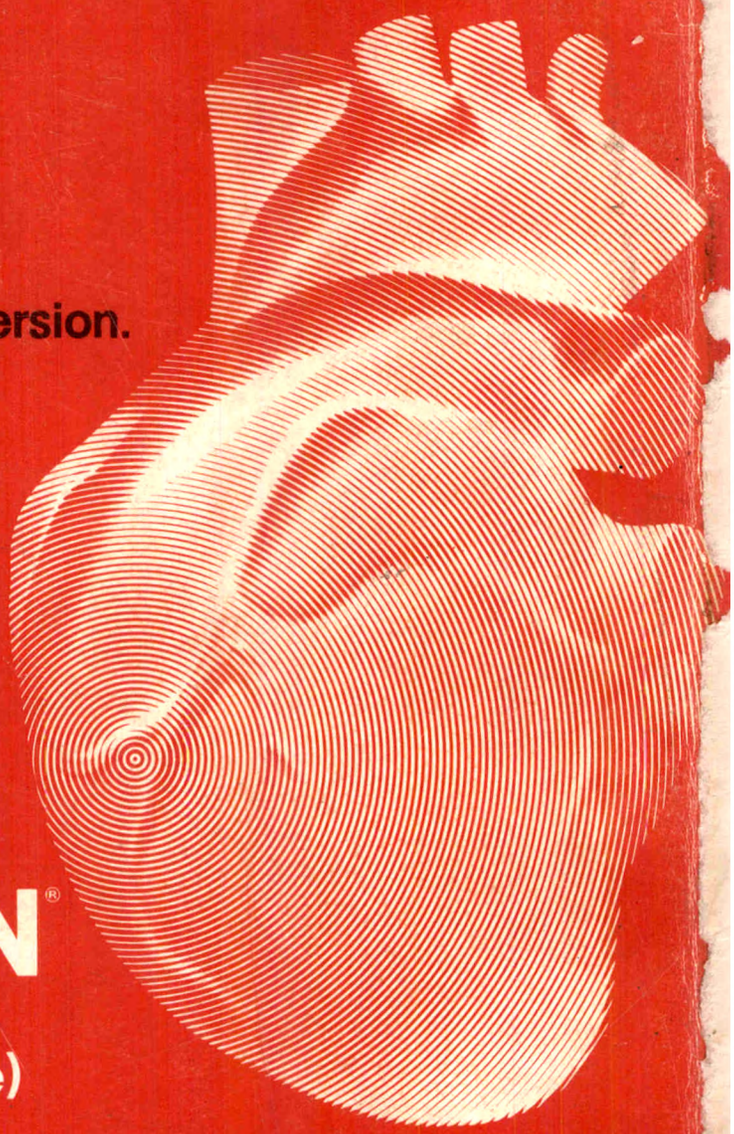
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